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≡ EP-657426

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(21) (A1)	2,132,887
(22)	1994/09/21
(43)	1995/04/23

(51) Int.Cl. ⁵ C07D-209/58; C07D-209/96; C07D-491/052; C07D-495/04;
A61K-031/40

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Tricyclic 1-Aminoethylpyrrole-Derivatives

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(30) (CH) 3202/93 1993/10/22
(CF) 2529/94 1994/08/17

(57) 24 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.



Industrie Canada Industry Canada

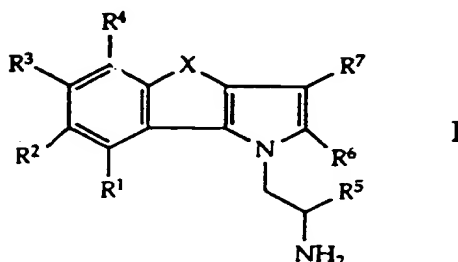
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Abstract

5

The present invention relates to tricyclic pyrrole derivatives of the general formula



10

wherein

R¹ to R⁴ each signify hydrogen, halogen, lower alkyl, phenyl, cycloalkyl or lower alkoxy and R² additionally signifies lower alkoxycarbonyl, acyloxy or mesyloxy;

15

R⁵ to R⁷ each signify hydrogen or lower alkyl;
X signifies -CH₂CH(C₆H₅)-, -CH=C(C₆H₅)-, -YCH₂-, -CH=CH- or -(CR¹¹R¹²)_n;

R¹¹ and R¹² each signify hydrogen, phenyl, lower alkyl or halogen;

20

n signifies 1 to 3 and

Y signifies O or S,

as well as pharmaceutically usable salts of basic compounds of formula I with acids.

25

These compounds and salts are novel and are distinguished by valuable pharmacological properties.

They can be used in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders,

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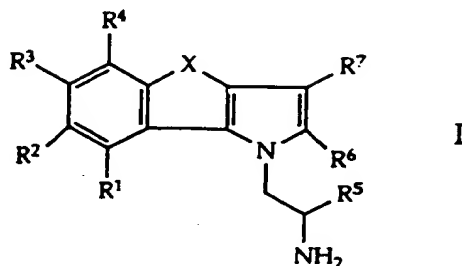
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psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

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RAN 4081/88

The present invention relates to tricyclic pyrrole derivatives, in particular it is concerned with pyrrole derivatives of the general formula



10 wherein

R¹ to R⁴

each signify hydrogen, halogen, lower alkyl, phenyl, cycloalkyl or lower alkoxy and R² additionally signifies lower alkoxycarbonyl, acyloxy or mesyloxy;

15 R⁵ to R⁷

each signify hydrogen or lower alkyl;

X

signifies -CH₂CH(C₆H₅)-, -CH=C(C₆H₅)-, -YCH₂-, -CH=CH- or -(CR¹¹R¹²)_n;

R¹¹ and R¹²

each signify hydrogen, phenyl, lower alkyl or halogen;

20 n

signifies 1 to 3 and

Y

signifies O or S,

as well as pharmaceutically usable salts of basic compounds of formula I with acids.

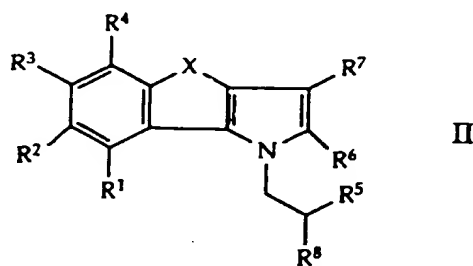
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These compounds and salts are novel and are distinguished by valuable pharmacological properties.

Objects of the present invention are compounds of general formula I and pharmaceutically acceptable salts thereof per se and as pharmaceutically active substances, the manufacture of the compounds and salts of general formula I, medicaments which

contain these compounds and salts of formula I and the manufacture of these medicaments, as well as the use of compounds of general formula I and of pharmaceutically usable salts thereof in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility and, respectively, for the manufacture of corresponding medicaments.

Furthermore, the compounds of the general formula



wherein R¹ to R⁷ and X have the significances given above and R⁸ signifies a residue convertible into an amino group or a hydroxy group, are objects of the invention.

These compounds are important intermediates for the manufacture of the pharmaceutically valuable compounds of general formula I.

The term "lower" used in present description denotes residues with a maximum of 7, preferably up to 4, carbon atoms,

"alkyl" denotes straight-chain or branched, saturated hydrocarbon residues such as methyl, ethyl, propyl, isopropyl or t-butyl, and "alkoxy" denotes an alkyl group attached via an oxygen atom, "halogen" can signify Cl, Br, F or I.

5

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like.

R⁵ can conveniently signify lower-alkyl, preferably methyl.

Compounds in which R⁵ signifies hydrogen are also preferred.

When R⁵ signifies methyl, compounds in which R¹, R³ and R⁴ signify hydrogen and R² signifies halogen, lower alkyl or methoxy are especially preferred.

Some particularly preferred representatives of the class of substance defined by general formula I in the scope of the present invention are:

25

(S)-2-(4,4,7-Trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(7-brom-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

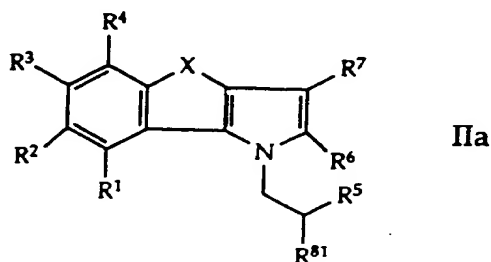
(S)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine,

(S)-2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine.

5

Compounds of general formula I as well as their pharmaceutically acceptable salts can be manufactured in accordance with the invention by

- 10 a) converting a compound of the general formula



- 15 wherein R^1 to R^7 and X have the significances given above and R^{81} signifies a residue convertible into an amino group, into a corresponding amino compound and

- b) if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

20

The compounds of general formula IIa in which R^{81} signifies a residue convertible into an amino group, preferably an azido group, an acetylamino group or another protected amino group, can be prepared according to methods known per se as described in more detail below. When the residue R^{81} is an azido group, the manufacture of the compounds of formula I effected is by reduction. This can be carried out with complex hydrides such as e.g. lithium aluminium hydride or by catalytic hydrogenation on metal catalysts such as e.g. platinum or palladium. When lithium aluminium hydride is used as the reducing agent, anhydrous ether or tetrahydrofuran is the most suitable solvent. Conveniently, this can be carried out as follows: after the dropwise addition of the compound of formula IIa in which R^{81} signifies an azido group to a solution consisting of the anhydrous solvent and the hydride,

the mixture is boiled at reflux, subsequently hydrolyzed with aqueous ether or THF solution and the aluminium hydroxide and lithium hydroxide precipitate is extracted with aqueous ether or THF solution.

5

The catalytic hydrogenation on metal catalysts, e.g. platinum or palladium, is conveniently effected at room temperature. Especially suitable solvents for this purpose are: water, alcohols, ethyl acetate, dioxan or mixtures of these solvents. The
10 hydrogenation is effected under a hydrogen atmosphere, conveniently in an autoclave or in a shaking apparatus. When R⁸¹ signifies an acetylamino group or another protected amino group such as e.g. trifluoromethylcarbonylamino, conversion into the corresponding amino compound is effected by hydrolysis.

15

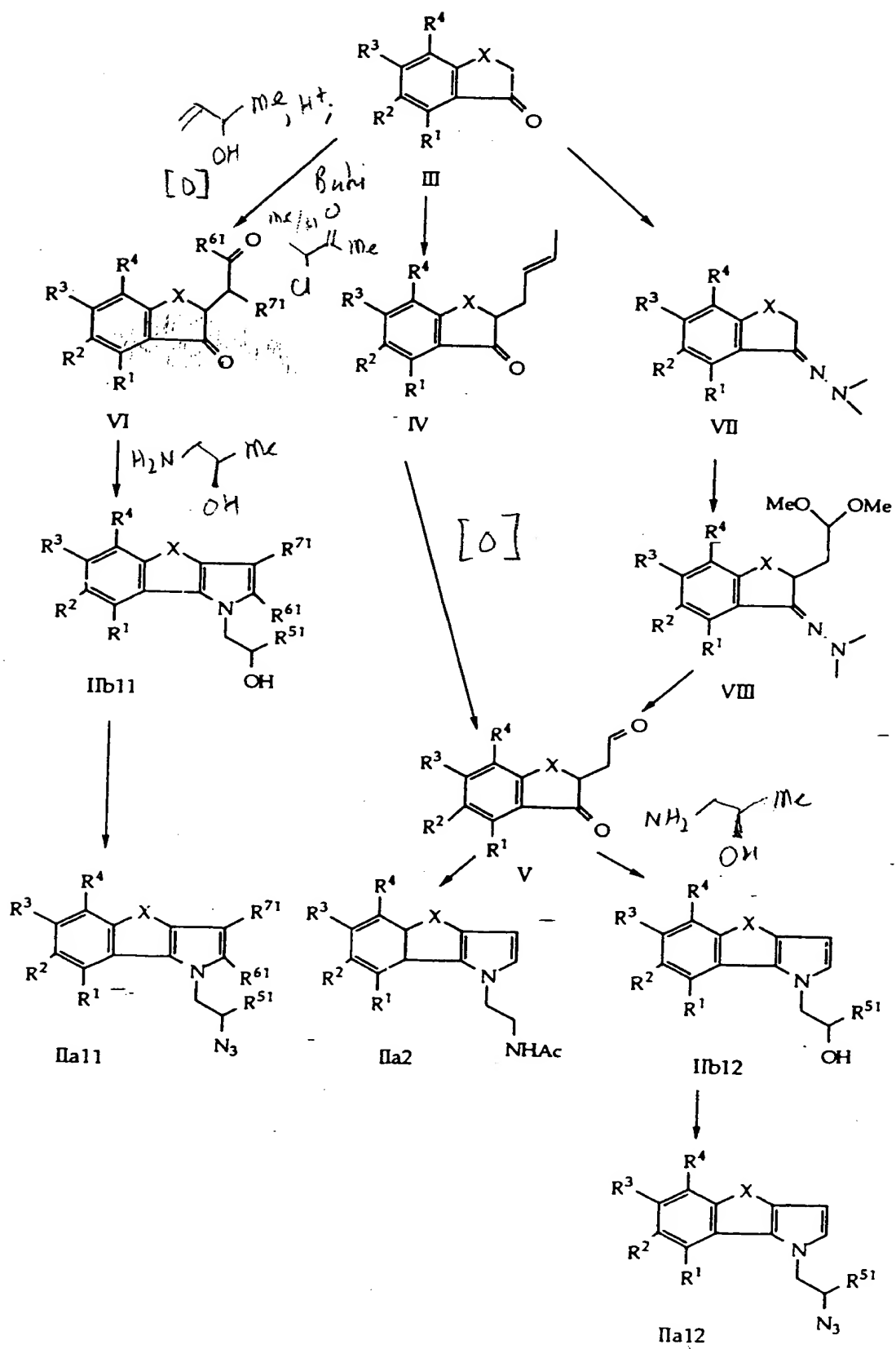
The hydrolysis to the corresponding amino compounds of general formula I is effected according to methods known per se. Metal hydroxides, for example sodium hydroxide or potassium hydroxide, which hydrolyze to the compounds of formula I in the
20 presence of water and a water-miscible organic solvent such as ethylene glycol or the like, are suitable for this purpose.

The conversion of the compounds of formula I into their corresponding acid addition salts is effected in the last
25 operation, i.e. after the hydrogenation or hydrolysis without isolating the compounds of formula I.

The fumaric acid salts are especially well suited for pharmaceutical use on stability grounds. However, all other acids
30 mentioned in the description also form pharmacologically acceptable salts. The salt formation is effected at room temperature, alcohol-ether mixtures are especially suitable as the solvent.

The preparation of the intermediates of formula II which
35 are required for the synthesis of the compounds of general formula I is presented in Scheme 1. In this, all substituents R¹ to R⁴ have the significances given in formula I. R⁵¹, R⁶¹ and R⁷¹ signify methyl. Me signifies methyl and Ac is acetyl. X likewise

has the significance given in formula I, except $-\text{CH}=\text{CH}-$; the preparation of corresponding compounds in which X signifies $-\text{CH}=\text{CH}-$ is shown in Scheme 2.

Scheme 1

The preparation of the compounds of IIa2 starting from compound III is conveniently effected as follows:

A compound of formula III is heated under reflux with 3-
5 buten-2-ol, 2,2-dimethoxypropane and catalytic amounts of p-
toluenesulphonic acid in anhydrous toluene. In a further variant,
2,2-dimethoxypropane replaces toluene as the solvent. In this
case, the reaction mixture is heated at reflux on a water
separator which is filled with molecular sieve. Subsequently, the
10 thus-obtained compounds of formula IV are converted into the
corresponding oxo-ethyl compounds. For this purpose, the
compound IV is dissolved in an anhydrous solvent, for example in
dichloromethane and methanol, and treated with a stream of
ozone at about -70°C. The compound of formula V can then be
15 cyclized to the pyrrole-acetamino compounds. Conveniently, N-
acetylenediamine is used and toluene or acetic acid is used
as the solvent. After reaction and purification have been carried
out the acetyl group can be cleaved off as described and the
compound of formula IIa2 can be converted into a compound of
20 formula I.

The hydroxy compound of formula IIb12 conveniently results
starting from the compounds of formula V by cyclization with 1-
amino-2-propanol in anhydrous toluene with catalytic amounts of
25 p-toluenesulphonic acid by heating on a water separator. Subse-
quently, the hydroxy group can be converted into a leaving group
according to methods known per se, for example by conversion
with a sulphonic acid chloride, preferably methanesulphonyl
chloride, into the sulphonate. By treatment with an azide, prefer-
30 ably sodium azide, in a polar solvent such as e.g. DMF, compounds
of formula IIb12 can be converted into the corresponding azido
compounds of formula IIa12 which, as described, can be converted
by reduction of the azido group into compounds of formula I.

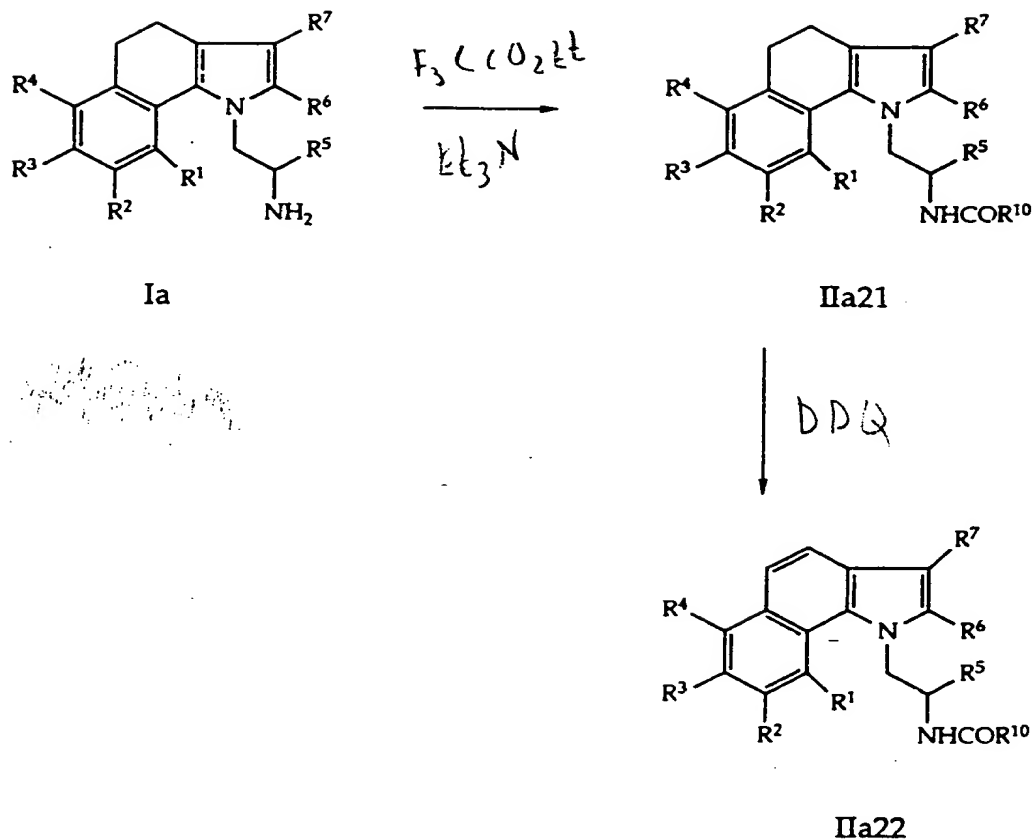
35 The compounds of formula V can also be prepared by another
route in accordance with Scheme 1.

A compound of formula III is conveniently heated with N,N-dimethylhydrazine under argon and then distilled over a Vigreux column. The compound of formula VII obtained is treated with DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) and
5 dissolved in anhydrous THF, cooled to about -75°C and subsequently treated with n-butyllithium in hexane as well as bromoacetaldehyde dimethyl acetal.

The resulting compound of formula VIII is subsequently
10 converted into the compound of formula V, after which an addition of phosphate buffer and copper(II) chloride dihydrate in THF is effected.

Compounds of formula IIb11 can also be prepared according
15 to Scheme 1. These compounds can then be converted as described into the compounds of formula I. Conveniently, the following procedure can be followed: a compound of formula III dissolved in anhydrous THF is treated with diisopropylamine and n-butyllithium and subsequently treated with chloroacetone or 3-chloro-
20 2-butanone. The resulting compounds VI are heated on a water separator in anhydrous toluene with catalytic amounts of p-toluenesulphonic acid. Treatment with 1-amino-2-propanol then leads to the compounds of formula IIb11.

25 Scheme 2 shows the preparation of compounds of formula IIa22 in which R¹ to R⁷ have the significances given above and X signifies -CH=CH-. R¹⁰ can be a methyl or trifluoromethyl group.

Scheme 2

5 The following procedure is conveniently followed:

A compound of formula Ia is reacted in a solution consisting
 of triethylamine and ethyl trifluoroacetate in an anhydrous
 solvent, preferably methanol, and after drawing off the solvent
 10 the residue is taken up in dioxan and treated with DDQ (2,3-
 dichloro-5,6-dicyano-1,4-benzoquinone). Subsequently, the
 protecting group can be cleaved off from the amino group as
 described.

15 As mentioned earlier, the compounds of formula I and their
 pharmaceutically acceptable salts possess valuable pharmaco-
 logical properties. They have the capacity to bind to serotonin
 receptors and are accordingly suitable for the treatment or
 prevention of illnesses or disorders of the kind referred to
 20 earlier and, respectively, for the manufacture of corresponding
 medicaments.

The binding of compounds of formula I in accordance with the invention to serotonin receptors was determined in vitro by standard methods. The preparations were investigated in accordance with the assays given hereinafter:

Method I:

- a) For the binding to the 5HT_{1A} receptor in accordance with the ³H-8-OH-DPAT binding assay according to the method of S.J. Peroutka, Biol. Psychiatry 20, 971-979 (1985).
- b) For the binding to the 5HT_{2C} receptor in accordance with the ³H-mesulergine binding assay according to the method of A. Pazos et al., Europ. J. Pharmacol. 106, 539-546 or. D. Hoyer, Receptor Research 8, 59-81 (1983).
- c) For the binding to the 5HT_{2A} receptor in accordance with the ³H-ketanserine binding assay according to the method of J.E. Leysen, Molecular Pharmacology 21, 301-304 (1981).

The IC₅₀ values of the test substances were determined, i.e. that concentration in nm by which 50% of the receptor-bound ligands are displaced.

The thus-determined activity of some compounds in accordance with the invention as well as those of some comparative compounds will be evident from the following Table:

Test methods

	1A a	2C b	2D c
Buspirone	19.50	3700.0	990.0
5 NAN-190	0.56	1800.0	581.0
5HT	1.50	9.5	1730.0
Metergoline	4.80	5.5	64.9
mCPP	227.00	53.0	319.0
RU 24969	8.0	159.0	2500.0
10 CP 93129	1620.00	2780.0	29200.0
Ritanserine	5750.00	37.0	3.1
Pirenperone	2879.00	37.0	2.9
3	2830 248	11.4 190	2160
4	3230	49.3	2170
15 5	2560	20.2	591
7	2160 90	24.0 50	1200
21	1350	56.6 46	2540
22	1590	30.4 25	1400
23	347 7.6	45.2 72	3340
20 28	1070	78.7	1630
30	298	58.1	479
31	337	28.1	874
32	139 7.8	18.0 92	1666
34	1620	107.0	2640
25 53	1100	308.0	11300
54	825	116.0	2590
55	1260	371.0	8350
59	97 4.0	23.8 64	1510
64	384	85.4	773
30 67	1750	146.0	1070
69	3460	143.0	854

- 3 = (S)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine
- 5 4 = (S)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine
- 5 = (S)-2-(8-methoxy-4,5-dihydro-1H-benz[g]indol-1-yl)-1-methyl-ethylamine
- 10 7 = (S)-2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine
- 21 = (RS)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine
- 15 22 = (RS)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine
- 20 23 = 2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethylamine
- 28 = (R)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine
- 25 30 = (R)-2-(8-methoxy-4,5-dihydro-1H-benz[g]indol-1-yl)-1-methyl-ethylamine
- 31 = (R)-2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine
- 30 32 = 2-(8-methoxy-1H-benz[g]indol-1-yl)-ethylamine
- 34 = (RS)-1-(1,4-dihydro[1]benzopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine
- 35 53 = (RS)-2-(6-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine

54 = (RS)-1-(8-methoxy-1,4-dihydro[1]benzopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine

5 55 = (RS)-2-(6-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine

59 = 2-(8-methoxy-4,5-dihydro-1H-benz[g]indol-1-yl)-ethylamine

10 64 = (RS)-1-(1,4-dihydro[1]benzothiopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine

67 = (RS)-2-(8-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine

15

69 = (2RS/4RS)-2-(4-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine

Method II:



20

a) Displacement tests with [3H]-5-HT(1 nM) as the radioligand on recombinant human-5HT_{1A} receptors expressed in 3T3 cells of mice were carried out in order to determine the affinity of a compound to the 5HT_{1A} receptor. Membranes which had been
25 obtained from 2 x 10⁵ cells were used as were various concentrations of the respective test compound.

b) For the binding to the 5HT_{2C} receptor in accordance with the [3H]-5-HT binding assay according to the method of S.J Peroutka
30 et al., Brain Research 584, 191-196 (1992).

c) For the binding to the 5HT_{2A} receptor in accordance with the [3H]-DOB binding assay according to the method of T. Branchek et al., Molecular Pharmacology 38, 604-609 (1990).

35

The p_{ki} values (p_{ki} = -log¹⁰ K_i) of the test substances are given. The k_i value is defined by the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{K_D}}$$

in which the IC_{50} values are those concentrations of test compounds in nm by which 50% of the receptor-bound ligands are displaced. [L] is the concentration of ligand and the K_D value is the dissociation constant of the ligand.

The thus-determined activity of some compounds in accordance with the invention will be evident from the following Table:

Test method

	a	b	c
1	5.66	8.49	7.27
2	5.39	9.44	8.03
3		8.16	7.12
8	5.34	8.63	7.18
9	5.56	8.29	7.46
12	5.00	8.00	6.94
14	5.00	7.78	7.62
17	5.00	7.74	6.25
25	5.00	7.38	6.26
26	5.25	7.58	7.17
37	5.32	7.45	6.51
44	5.73	7.10	6.57
50	5.62	6.97	6.35

15 1 = (S)-2-(4,4,7-Trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1)

2 = (S)-2-(7-Methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1)

20

8 = (S)-2-(7-Ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1)

- 9 = (S)-2-(7-Fluor-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1)
- 12 = (S)-2-(7-Methoxy-4,4-diethyl-1,4-dihydro-indeno-
5 [1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5)
- 14 = (S)-2-(7-Phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-
1-methyl-ethylamine fumarate (1:0.5)
- 10 17 = (S)-2-(7-Ethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-
methyl-ethylamine fumarate (1:0.5)
- 25 = (S)-2-(6,7-Difluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-
yl)-1-methyl-ethylamine fumarate (1:0.5)
- 15 26 = (S)-2-(6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-
indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine-fumarate
(1:0.5)
- 20 37 = (RS)-2-(5-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-
1-methyl-ethylamine fumarat (1:0.5)
- 44 = (S)-1-Methyl-2-(7'-methyl-1',4'-dihydro-spiro[cyclo-
pentane-1,4'-indeno[1,2-b]pyrrol]-1-yl)-ethylamine
25 fumarate (1:1)
- 50 = (RS)-2-(5-Methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-
1-methyl-ethylamine fumarate (1:0.5)

30

Penile erection (rats)

It has been shown that penile erection is dependent on the stimulation of the 5HT_{2C} receptor (see Berendsen & Broekkamp, Eur.J.Pharmacol, 135, 179-184 (1987)).

35

The number of penile erections was determined within 45 minutes following administration of the test substance to the

animal. The ED₅₀ is that dosage which brings about 50% of these erections.

Example No.	ED ₅₀ (mg/kg, s. c.)
1	0.90
2	0.50
3	1.20
4	2.70
5	3.20

5 The compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard
10 and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions, or nasally.

15 For the manufacture of pharmaceutical preparations, the compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or
20 its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers
25 are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid
30 polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants.

5 They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salt thereof and a

10 therapeutically inert carrier are also an object of the present invention, as is a process for their manufacture which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts thereof into a galenical administration form together with one or more therapeutically

15 inert carriers.


In accordance with the invention compound of general formula I as well as their pharmaceutically acceptable acid addition salts can be used in the treatment or prevention of

20 central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states,

25 mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis,

30 stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility and, respectively, for the manufacture of corresponding medicaments. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In the case of oral administration the dosage lies in a range of about 0.01 mg per dose to

35 about 500 mg per day of a compound of general formula I or the corresponding amount of a pharmaceutically acceptable acid



addition salt thereof, although the upper limit can also be exceeded when this is found to be indicated.

The following Examples illustrate the present invention in more detail. However, they are not intended to limit its scope in any manner. All temperatures are given in degrees celsius

Example 1

10 a) A solution of 18.9 g (108 mmol) of 3,3,6-trimethyl-1-indanone, 22.4 ml (0.26 mol) of 3-buten-2-ol and 300 mg of p-toluenesulphonic acid in 200 ml of 2,2-dimethoxy-propane was boiled under reflux for 64 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction
15 mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 6:1). In addition to 4.5 g of educt there were obtained 12.7 g (51%) of (RS)-2-(2-buten-1-yl)-3,3,6-trimethyl-1-indanone as a yellow oil

20 b) An ozone stream (2.5 g ozone/hour) was conducted for 60 minutes while stirring through a solution, cooled to -70° of 12.7 g (55.6 mmol) (RS)-2-(2-buten-1-yl)-3,3,6-trimethyl-1-indanone in 200 ml of anhydrous dichloromethane and 40 ml of
25 anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 6.12 ml (83.4 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 18 hours. The reaction mixture was evaporated in a vacuum, the residue was
30 treated with 150 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 2.5 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further
35 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 11.3 g (94%)

of (RS)-2-(2-oxoethyl)-3,3,6-trimethyl-1-indanone as a light yellow oil.

c) A solution of 2.16 g (10 mmol) of (RS)-2-(2-oxoethyl)-3,3,6-trimethyl-1-indanone and 80 ml of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:2). 1.5 g (59%) of (R)-1-(4,4,7-trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 0.91 ml (11.7 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.5 g (5.87 mmol) of (R)-1-(4,4,7-trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.27 ml (23.5 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green solid obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.76 g (11.7 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on

silica gel (hexane/ethyl acetate 4:1). 1.13 g (68%) of (S)-1-(2-azido-propyl)-4,4,7-trimethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a reddish oil.

- 5 e) 1.1 g (3.92 mmol) of (S)-1-(2-azido-propyl)-4,4,7-trimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 110 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum.
- 10 The colourless oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 455 mg (3.92 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 24 hours and the white crystals were subsequently filtered off. 805 mg (77%)
- 15 of (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 196° were obtained.

Example 2

20

- a) A solution of 12.1 g (63.7 mmol) of 6-methoxy-3,3-dimethyl-1-indanone, 11.1 ml (0.13 mol) of 3-buten-2-ol and 110 mg of p-toluenesulphonic acid in 110 ml of 2,2-dimethoxypropane was boiled under reflux for 67 hours on a water
- 25 separator filled with molecular sieve (0.4 nm, 2mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). In addition to 4.64 g of educt there were obtained 5.86 g (38%) of (RS)-2-(2-buten-1-yl)-6-
- 30 methoxy-3,3-dimethyl-1-indanone as a yellow oil.

- b) An ozone stream (3 g ozone/hour) was conducted for 40 minutes while stirring through a solution, cooled to -70°, of 5.86 g (24 mmol) of (RS)-2-(2-buten-1-yl)-6-methoxy-3,3-
- 35 dimethyl-1-indanone in 100 ml of anhydrous dichloromethane and 20 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2.64 ml (36 mmol) of di-

methyl sulphide the mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 60 ml of dichloromethane and, after the addition of 10 ml of water and 10 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 4.94 g (89%) of (RS)-2-(2-oxoethyl)-6-methoxy-3,3-dimethyl-1-indanone were obtained as a light yellow oil.

c) A solution of 4.94 g (21.3 mmol) of (RS)-2-(2-oxoethyl)-6-methoxy-3,3-dimethyl-1-indanone and 220 ml of p-toluenesulphonic acid in 200 ml of anhydrous toluene was heated on a water separator. A solution of 6.39 g (85.2 mmol) of (R)-1-amino-2-propanol in 40 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes, during which the solvent was reduced to a volume of 40 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 3.42 g (60%) of (R)-1-(7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)propan-2-ol were obtained as a brown oil.

d) 2.0 ml (25.4 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 3.42 g (12.7 mmol) of (R)-1-(7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)propan-2-ol and 7.3 ml (50.8 mmol) of triethylamine in 70 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 170 ml of dichloromethane, washed twice with 90 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 90 ml of saturated sodium chloride solution, dried over mag-

nesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 70 ml of anhydrous dimethylformamide, treated with 1.35 g (20.4 mmol) of sodium azide and the reaction mixture was heated to 60° for 20 hours while stirring.

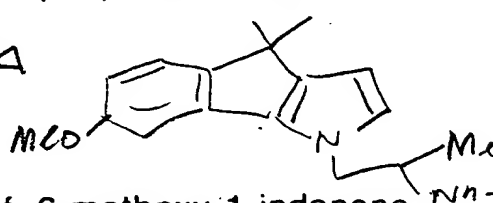
- 5 After cooling the solution was poured into 100 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was
10 concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 1.89 g (50%) of (S)-1-(2-azido-propyl)-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a yellow oil.

15

- e) 1.89 g (63.8 mmol) of (S)-1-(2-azido-propyl)-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 190 mg of platinum oxide for 2 hours. The catalyst was subsequently
20 filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated with a solution of 740 mg (6.38 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 15 hours and the
25 white crystals were subsequently filtered off. 1.46 g (60%) of (S)-2-(7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 181° were obtained.

30

Example 3



- a) A solution of 9.3 g (57.3 mmol) of 6-methoxy-1-indanone, 11.8 ml (0.14 mol) of 3-buten-2-ol and 100 mg of p-toluenesulphonic acid in 100 ml of 2,2-dimethoxypropane was boiled
35 under reflux for 64 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1).

9.2 g (74%) of (RS)-2-(2-buten-1-yl)-6-methoxy-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 80 minutes while stirring through a solution, cooled to -70° , of 15.2 g (70.3 mmol) of (RS)-2-(2-buten-1-yl)-6-methoxy-1-indanone in 250 ml of anhydrous dichloromethane and 50 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 7.75 ml (105 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 250 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 150 ml of water and neutralized while stirring by the spatula-wise addition of sodium hydrogen carbonate. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was crystallized from diethyl ether/hexane. 12 g (83%) of (RS)-2-(2-oxoethyl)-6-methoxy-1-indanone were obtained as a light yellow solid with m.p. 59° .

c) A solution of 2 g (9.8 mmol) of (RS)-2-(2-oxoethyl)-6-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.94 g (39.2 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 1.5 g (63%) of (R)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a solid with m.p. 75° .

d) 0.96 ml (12.3 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.5 g (6.2 mmol) of (R)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-propan-2-ol and 3.45 ml (24.6 mmol) of triethyl-
5 amine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were
10 extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 60 ml of anhydrous dimethylformamide, treated with 0.77 g (11.8 mmol)
15 of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium
20 chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.0 g (60%) of (S)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno-
[1,2-b]pyrrole was obtained as a colourless oil.

25 e) 1 g (3.7 mmol) of (S)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 100 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with
30 ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous ether, filtered and treated while stirring with a solution of 240 mg (2.07 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white
35 crystals were subsequently filtered off. 870 mg (77%) of (S)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 206° were obtained.

Example 4

- a) A solution of 20.2 g (0.12 mol) of 6-chloro-1-indanone, 25 ml (0.29 mol) of 3-buten-2-ol and 200 mg of p-toluenesulphonic acid in 25 ml of 2,2-dimethoxypropane and 200 ml of anhydrous toluene was boiled under reflux for 16 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 5:1). 10.3 g (39%) of (RS)-2-(2-buten-1-yl)-6-chloro-1-indanone were obtained as a yellow oil.
- b) An ozone stream (3 g ozone/hour) was conducted for 45 minutes while stirring through a solution, cooled to -70° , of 10.3 g (46.7 mmol) of (RS)-2-(2-buten-1-yl)-6-chloro-1-indanone in 200 ml of anhydrous dichloromethane and 100 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 5.13 ml (70 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 18 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 60 ml of dichloromethane and, after the addition of 15 ml of water and 15 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was recrystallized from ethyl acetate/hexane. 8.29 g (85%) of (RS)-2-(2-oxoethyl)-6-chloro-1-indanone were obtained as a white solid with m.p. 80° .
- c) A solution of 2.5 g (12.0 mmol) of (RS)-2-(2-oxoethyl)-6-chloro-1-indanone and 100 mg of p-toluenesulphonic acid in 120 ml of anhydrous toluene was heated on a water separator. A solution of 3.6 g (47.9 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling

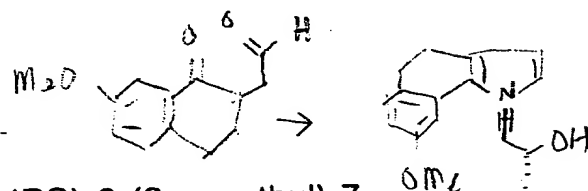
solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.42 g (81%) of (R)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil which was used directly in the next reaction.

d) 1.53 ml (19.54 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.42 g (9.8 mmol) of (R)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 5.48 ml (39.1 mmol) of triethylamine in 70 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 1.27 g (19.54 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time and once with 70 ml of ethyl acetate. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.5 g (56%) of (S)-1-(2-azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as an oil.

e) 1.5 g (5.5 mmol) of (S)-1-(2-azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 150 mg of platinum oxide for 14 hours. The catalyst was subsequently filtered off, rinsed with

ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 306 mg (2.64 mmol) of methanol. The mixture was stirred at room temperature for 3 hours and the white crystals were subsequently filtered off. 1.12 g (67%) of (S)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 197° were obtained.

Example 5

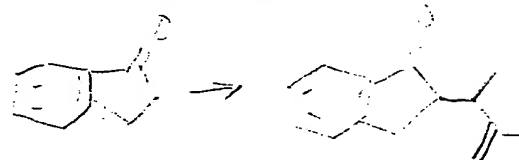


- a) A solution of 2 g (9.2 mmol) of (RS)-2-(2-oxoethyl)-7-methoxy-1-tetralone and 100 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 2.78 g (37 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.25 g (94%) of (R)-1-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-propan-2-ol were obtained as a brown oil which was used directly in the next reaction.
- b) 1.4 ml (18 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°C, of 2.25 g (9 mmol) of (R)-1-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-propan-2-ol and 5 ml (36 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 300 ml of diethyl ether, washed twice with 100 ml of saturated sodium hydrogen carbonate solution and the combined aqueous phases were extracted once with 100 ml of diethyl ether. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethyl formamide, treated with 1.17 g (18 mmol) of sodium azide and the

reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.78 g (71%) of (S)-1-(2-azido-propyl)-4,5-dihydro-8-methoxy-1H-benz[g]indole were obtained as a colourless oil.

c) 2.78 g (9.8 mmol) of (S)-1-(2-azido-propyl)-4,5-dihydro-8-methoxy-1H-benz[g]indole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 280 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. 700 mg (2.7 mmol) of the colourless oil obtained were dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 317 mg (2.7 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 2 hours and the white crystals were subsequently filtered off. 820 mg (81%) of (S)-2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 193° were obtained.

Example 6



a) A solution of 19.7 g (0.13 mol) of 6-fluoro-1-indanone, 27.0 ml (0.31 mol) of 3-buten-2-ol and 200 mg of p-toluene-sulphonic acid in 200 ml of 2,2-dimethoxypropane was boiled under reflux for 67 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 18.9 g (71%) of (RS)-2-(2-buten-1-yl)-6-fluoro-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 100 minutes while stirring through a solution, cooled to -70° , of 18.9 g (92.5 mmol) of (RS)-2-(2-buten-1-yl)-6-fluoro-1-indanone in 300 ml of anhydrous dichloromethane and 60 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 102 ml (140 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 300 ml of dichloromethane and, after the addition of 43 ml of water and 43 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was crystallized from diethyl ether/hexane. 16.5 g (92%) of (RS)-2-(2-oxo-ethyl)-6-fluoro-1-indanone were obtained as a white solid with m.p. 62° .

c) A solution of 1.92 g (10 mmol) of (RS)-2-(2-oxo-ethyl)-6-fluoro-1-indanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 1.73 g (75%) of (R)-1-(7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil which was used without further purification in the next reaction.

d) 1.17 ml (15.0 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0° , of 1.73 g (7.5 mmol) of (R)-1-(7-fluoro-1,4-dihydro-indeno[1,2-

b]pyrrol-1-yl)-propan-2-ol and 4.2 ml (29.9 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of diethyl ether, washed
5 twice with 60 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated
10 in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 973 mg (15.0 mmol) of sodium azide and the reaction mixture was heated to 50° for 15 hours while stirring. After cooling the solution was poured into 110 ml of water and extracted twice with 110 ml of diethyl
15 ether each time and once with 60 ml of ethyl acetate. The combined organic phases were washed once with 80 ml of water and once with 80 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chroma-
20 tography on silica gel (toluene). 750 mg (39%) of (S)-1-(2-azido-propyl)-7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a colourless oil.

e) 750 mg (2.9 mmol) of (S)-1-(2-azido-propyl)-7-fluoro-
25 1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 40 ml of anhydrous ethanol were hydrogenated on 75 mg of platinum oxide for 15 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl
30 ether, filtered and treated while stirring with a solution of 370 mg (1.46 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 3 hours and the white crystals were subsequently filtered off. 460 mg (54%) of (S)-2-(7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-
35 methyl-ethylamine fumarate (1:0.5) m.p. 194° were obtained.

Example 7

- a) A solution of 1.5 g (5.9 mmol) of (S)-2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine, 0.74 g
5 (7.3 mmol) of triethylamine and 1.04 g (7.3 mmol) of ethyl trifluoroacetate in 100 ml of anhydrous methanol was stirred at room temperature for 27 hours. After the solvent had been drawn off in a vacuum the residue was taken up with 100 ml of anhydrous dioxan, 1.56 g (6.9 mmol) of DDQ were added and the
10 mixture was boiled under reflux for 1.5 hours. Subsequently, the reaction mixture was concentrated in a vacuum and the residue was purified by column chromatography on silica gel (dichloromethane/acetone 4:1). 1.2 g (59%) of (S)-N-[2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethyl]-trifluoroacetamide were
15 obtained as a pale brown solid which was used in the next reaction without further recrystallization.
- b) A mixture of 1.2 g (3.4 mmol) of (S)-N-[2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethyl]-trifluoroacetamide, 1.2 g
20 (21 mmol) of potassium hydroxide in 3 ml of water and 50 ml of methanol was boiled under reflux for 3 hours. The reaction mixture was subsequently poured into 100 ml of 1N sodium hydroxide solution, extracted twice with 100 ml of diethyl ether each time and once with 100 ml of ethyl acetate, the combined
25 organic phases were washed once with 150 ml and dried over magnesium sulphate. After concentration in a vacuum the residue was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 398 mg (3.4 mmol) of fumaric acid in 30 ml of methanol. The mixture was stirred at
30 room temperature for 16 hours and the white crystals were subsequently filtered off. 780 mg (73%) of (S)-2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 208° were obtained.

Example 8

- a) A solution of 9.1 g (48.3 mmol) of 6-ethyl-3,3-dimethyl-1-indanone, 9.98 ml (0.12 mol) of 3-buten-2-ol and 250 mg of p-toluenesulphonic acid in 100 ml of 2,2-dimethoxypropane was boiled under reflux for 88 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 6:1). In addition to 2.0 g of educt there were obtained 8.2 g (70%) of (RS)-2-(2-buten-1-yl)-6-ethyl-3,3-dimethyl-1-indanone as a yellow oil.
- b) An ozone stream (3 g ozone/hour) was conducted for 40 minutes while stirring through a solution, cooled to -70° , of 8.2 g (33.8 mmol) of (RS)-2-(2-buten-1-yl)-6-ethyl-3,3-dimethyl-1-indanone in 120 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 3.72 ml (50.7 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 100 ml of dichloromethane and, after the addition of 15 ml of water and 15 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 7.55 g (97%) of (RS)-2-(2-oxoethyl)-6-ethyl-3,3-dimethyl-1-indanone were obtained as a light yellow oil.
- c) A solution of 2.3 g (10.0 mmol) of (RS)-2-(2-oxoethyl)-6-ethyl-3,3-dimethyl-1-indanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-

- propanol in 40 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 3:2). 2.45 g (91%) of (R)-1-(7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a red oil.
- 10 d) 1.39 ml (17.9 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.4 g (8.91 mmol) of (R)-1-(7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 4.97 ml (35.6 mmol) of triethylamine in 50 ml of dichloromethane and the mixture
- 15 was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The
- 20 combined organic phases were washed with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 1.16 g (17.8 mmol) of sodium azide and the reaction mixture was heated
- 25 to 60° for 17 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium
- 30 sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 1.44 g (55%) of (S)-1-(2-azido-propyl)-7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a red oil.
- 35 e) 1.44 g (4.89 mmol) of (S)-1-(2-azido-propyl)-7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 140 mg of platinum

oxide for 1.5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 120 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution
5 of 568 mg (4.89 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 15 hours and the white crystals were subsequently filtered off. 1.04 g (55%) of (S)-2-(7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 178° were
10 obtained.

Example 9

15 a) A solution of 10.0 g (56.1 mmol) of 6-fluoro-3,3-dimethyl-1-indanone, 11.1 ml (0.13 mol) of 3-buten-2-ol and 200 mg of p-toluenesulphonic acid in 200 ml of 2,2-dimethoxypropane was boiled under reflux for 96 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in
20 a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 8:1). In addition to 11.9 g of educt there were obtained 3.38 g (26%) of (RS)-2-(2-buten-1-yl)-6-fluoro-3,3-dimethyl-1-indanone as a yellow oil.

25 b) An ozone stream (1.5 g ozone/hour) was conducted for 30 minutes while stirring through a solution, cooled to -70°, of 3.38 g (14.6 mmol) of (RS)-2-(2-buten-1-yl)-6-fluoro-3,3-dimethyl-1-indanone in 75 ml of anhydrous dichloromethane and 15 ml of anhydrous methanol. Subsequently, the mixture was
30 flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 1.6 ml (21.8 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 17 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 40 ml of dichloromethane and, after the addition of
35 5 ml of water and 5 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 90 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of

water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 3.04 g (95%) of (RS)-2-(2-oxoethyl)-6-fluoro-3,3-dimethyl-1-indanone were obtained as a light yellow oil.

c) A solution of 3.04 g (13.8 mmol) of (RS)-2-(2-oxoethyl)-6-fluoro-3,3-dimethyl-1-indanone and 110 mg of p-toluene-sulphonic acid in 100 ml of anhydrous toluene was heated on a water separator. A solution of 4.14 g (55.2 mmol) of (R)-1-amino-2-propanol in 40 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.0 g (56%) of (R)-1-(7-fluoro-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.27 ml (16.3 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.0 g (8.15 mmol) of (R)-1-(7-fluoro-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 4.52 ml (32.6 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 60 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 60 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 1.07 g (16.3 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 80 ml of water and extracted three times with 70 ml of ethyl acetate each time. The combined organic phases

were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.22 g (54%) of (S)-1-(2-azido-propyl)-7-fluoro-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a yellow oil.

e) 1.22 g (4.29 mmol) of (S)-1-(2-azido-propyl)-7-fluoro-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 120 mg of platinum oxide for 2 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 150 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 498 mg (4.29 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 15 hours and the white crystals were subsequently filtered off. 1.12 g (70%) of (S)-2-(7-fluoro-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 211° were obtained.

Example 10

a) A solution of 14.2 g (97.3 mmol) of 6-methyl-1-indanone, 20.1 ml (0.23 mol) of 3-buten-2-ol and 140 mg of p-toluene-sulphonic acid in 140 ml of 2,2-dimethoxypropane was boiled under reflux for 69 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 5:1). 16.3 g (83%) of (RS)-2-(2-buten-1-yl)-6-methyl-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 80 minutes while stirring through a solution, cooled to -70°, of 16.3 g (81.4 mmol) of (RS)-2-(2-buten-1-yl)-6-methyl-1-indanone in 300 ml of anhydrous dichloromethane and 60 ml of

anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 8.95 ml (122 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 300 ml of dichloromethane and, after the addition of 40 ml of water and 40 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. The crude product obtained was recrystallized from diethyl ether/hexane. 12.7 g (82%) of (RS)-2-(2-oxoethyl)-6-methyl-1-indanone were obtained as a light yellow solid with m.p. 53-54°.

c) A solution of 2.82 g (15 mmol) of (RS)-2-(2-oxoethyl)-6-methyl-1-indanone and 100 mg of p-toluenesulphonic acid in 100 ml of anhydrous toluene was heated on a water separator. A solution of 4.51 g (60 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.7 g (79%) of (R)-1-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown-green oil.

d) 1.8 ml (23.8 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.7 g (11.9 mmol) of (R)-1-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 6.7 ml (47.6 mmol) of triethylamine in 75 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of dichloromethane.

- washed twice with 90 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 90 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 70 ml of anhydrous dimethylformamide, treated with 1.55 g (23.8 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 150 ml of water and extracted twice with 150 ml of ethyl acetate each time. The combined organic phases were washed once with 120 ml of water and once with 120 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.5 g (50%) of (S)-1-(2-azido-propyl)-7-methyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a light yellow oil.
- e) 1.5 g (5.94 mmol) of (S)-1-(2-azido-propyl)-7-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 150 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 150 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 345 mg (2.97 mmol) of fumaric acid in 25 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 1.11 g (65%) of (S)-2-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 194° were obtained.

Example 11

35

- a) A solution of 10.0 g (47.4 mmol) of 6-bromo-1-indanone, 9.79 ml (0.11 mol) of 3-buten-2-ol and 100 mg of p-toluene-sulphonic acid in 100 ml of 2,2-dimethoxypropane was boiled

under reflux for 71 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 1:1). In addition to 3.07 g of educt there were obtained 9.86 g (78%) of (RS)-2-(2-buten-1-yl)-6-bromo-1-indanone as a yellow oil.

b) An ozone stream (2 g ozone/hour) was conducted for 60 minutes while stirring through a solution, cooled to -70° , of 9.86 g (37.2 mmol) of (RS)-2-(2-buten-1-yl)-6-bromo-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.09 ml (55.8 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 150 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. The crude product obtained was recrystallized from ethyl acetate/hexane. 7.5 g (80%) of (RS)-2-(2-oxoethyl)-6-bromo-1-indanone were obtained as a light yellow solid with m.p. 84° .

c) A solution of 2.0 g (7.9 mmol) of (RS)-2-(2-oxoethyl)-6-bromo-1-indanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 2.37 g (31.6 mmol) of (R)-1-amino-2-propanol in 10 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture

was purified by column chromatography on silica gel (diethyl ether/hexane 4:1). 1.19 g (52%) of (R)-1-(7-bromo-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

5

d) 0.63 ml (8.14 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.19 g (4.07 mmol) of (R)-1-(7-bromo-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.27 ml (16.3 mmol) of triethyl-
10 amine in 40 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases
15 were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.53 g
20 (8.14 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were
25 washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.95 g (74%) of (S)-1-(2-azido-propyl)-7-bromo-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a
30 colourless oil.

e) 0.95 g (2.99 mmol) of (S)-1-(2-azido-propyl)-7-bromo-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 40 ml of anhydrous ethanol were hydrogenated on 95 mg of platinum oxide for 4
35 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The product mixture was separated on silica gel (methanol/dichloromethane 5:95). The colourless oil obtained (507 mg) was dissolved in

50 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 101 mg (0.87 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently
5 filtered off. 503 mg (50%) of (S)-2-(7-bromo-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 197° were obtained.

Example 12

10

a) A solution of 22.0 g (101 mmol) of 6-methoxy-3,3-diethyl-1-indanone, 20.8 ml (0.24 mol) of 3-buten-2-ol and 220 mg of p-toluenesulphonic acid in 220 ml of 2,2-dimethoxypropane was boiled under reflux for 87 hours on a water
15 separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 6:1). In addition to 15.7 g of educt there were obtained 4.1 g (15%) of (RS)-2-(2-buten-1-yl)-6-methoxy-
20 3,3-diethyl-1-indanone as a yellow oil.

b) An ozone stream (2 g ozone/hour) was conducted for 25 minutes while stirring through a solution, cooled to -70°, of 4.1 g (15.1 mmol) of (RS)-2-(2-buten-1-yl)-6-methoxy-3,3-
25 diethyl-1-indanone in 60 ml of anhydrous dichloromethane and 15 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 1.66 ml (22.6 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 22 hours. The
30 reaction mixture was evaporated in a vacuum, the residue was treated with 50 ml of dichloromethane and, after the addition of 8 ml of water and 8 ml of trifluoroacetic acid, stirred at room temperature for 2.5 hours. The mixture was subsequently poured into 70 ml of water and neutralized by the spatula-wise addition
35 of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium

sulphate and concentrated in a vacuum. 3.9 g (99%) of (RS)-2-(2-oxoethyl)-6-methoxy-3,3-diethyl-1-indanone were obtained as a light yellow oil.

5 c) A solution of 3.9 g (15 mmol) of (RS)-2-(2-oxoethyl)-6-methoxy-3,3-diethyl-1-indanone and 120 mg of p-toluene-sulphonic acid in 100 ml of anhydrous toluene was heated on a water separator. A solution of 4.5 g (60 mmol) of (R)-1-amino-2-propanol in 30 ml of anhydrous toluene was added dropwise to
10 the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:1). 2.73 g (61%) of (R)-1-(7-methoxy-4,4-diethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol
15 were obtained as a red-brown oil.

d) 1.42 ml (18.2 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of
20 2.73 g (9.12 mmol) of (R)-1-(7-methoxy-4,4-diethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 5.08 ml (36.5 mmol) of triethylamine in 70 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with
25 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with
30 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 1.18 g (18.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 70 ml of water and
35 extracted three times with 80 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 80 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated

in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 2.33 g (79%) of (S)-1-(2-azido-propyl)-7-methoxy-4,4-diethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a yellow oil.

- 5 e) 2.25 g (6.94 mmol) of (S)-1-(2-azido-propyl)-7-methoxy-4,4-diethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 225 mg of platinum oxide for 2 hours. The catalyst was subsequently
10 filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 406 mg (3.5 mmol) of fumaric acid in 10 ml of
15 methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 1.93 g (78%) of (S)-2-(7-methoxy-4,4-diethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 189° were obtained.

20 Example 13

- a) A solution of 20.0 g (133 mmol) of 5-fluoro-1-indanone, 27.5 ml (0.32 mol) of 3-buten-2-ol and 200 mg of p-toluene-sulphonic acid in 200 ml of 2,2-dimethoxy-propane was boiled
25 under reflux for 63 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 18.6 g (68%) of (RS)-2-(2-buten-1-yl)-5-fluoro-1-indanone
30 were obtained as a yellow oil.

- b) An ozone stream (3.5 g ozone/hour) was conducted for 85 minutes while stirring through a solution, cooled to -70°, of 18.5 g (90.6 mmol) of (RS)-2-(2-buten-1-yl)-5-fluoro-1-
35 indanone in 300 ml of anhydrous dichloromethane and 50 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 9.9 ml (135 mmol) of dimethyl sulphide the mixture

was stirred at room temperature for 17 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 220 ml of dichloromethane and, after the addition of 40 ml of water and 40 ml of trifluoroacetic acid, stirred at room temperature for 4.5 hours. The mixture was subsequently poured into 170 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 110 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 170 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There was obtained a yellow oil which was crystallized from diethyl ether/hexane. 13.6 g (78%) of (RS)-2-(2-oxoethyl)-5-fluoro-1-indanone were obtained as a light yellow solid with m.p. 56°.

c) A solution of 2.88 g (15 mmol) of (RS)-2-(2-oxoethyl)-5-fluoro-1-indanone and 100 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 4.51 g (60 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.75 g (79%) of (R)-1-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.8 ml (23.8 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.75 g (11.9 mmol) of (R)-1-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 6.7 ml (47.6 mmol) of triethylamine in 70 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 90 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 90 ml of dichloromethane. The

combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 60 ml of anhydrous dimethylformamide, treated with 1.55 g (12.5 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 80 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.23 g (40%) of (S)-1-(2-azido-propyl)-6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a light yellow oil.

e) 1.23 g (4.80 mmol) of (S)-1-(2-azido-propyl)-6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 60 ml of anhydrous ethanol were hydrogenated on 125 mg of platinum oxide for 6 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 130 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 279 mg (2.40 mmol) of fumaric acid in 25 ml of methanol. The mixture was stirred at room temperature for 15 hours and the white crystals were subsequently filtered off. 1.0 g (72%) of (S)-2-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 200° were obtained.

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Example 14

a) A solution of 13.2 g (63.4 mmol) of 6-phenyl-1-indanone, 11 ml (0.13 mol) of 3-buten-2-ol and 110 mg of p-toluene-sulphonic acid in 110 ml of 2,2-dimethoxy-propane was boiled under reflux for 48 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified

by column chromatography on silica gel (hexane/diethyl ether 5:1). 12.0 g (72%) of (RS)-2-(2-buten-1-yl)-6-phenyl-1-indanone was obtained as a light yellow solid which was used without further purification in the next reaction.

5

b) An ozone stream (3 g ozone/hour) was conducted for 75 minutes while stirring through a solution, cooled to -70° , of 12.0 g (45.8 mmol) of (RS)-2-(2-buten-1-yl)-6-phenyl-1-indanone in 180 ml of anhydrous dichloromethane and 40 ml of
10 anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 5.04 ml (68.7 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was
15 treated with 120 ml of dichloromethane and, after the addition of 30 ml of water and 30 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further
20 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 11.2 g (97%) of (RS)-2-(2-oxoethyl)-6-phenyl-1-indanone were obtained as a
25 light yellow oil.

c) A solution of 2.5 g (10.0 mmol) of (RS)-2-(2-oxoethyl)-6-phenyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A
30 solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by
35 column chromatography on silica gel (diethyl ether/hexane 7:3). 1.5 g (52%) of (R)-1-(7-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 0.82 ml (10.4 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.5 g (5.2 mmol) of (R)-1-(7-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3 ml (20.8 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green solid obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.53 g (8.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 80 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.64 g (39%) of (S)-1-(2-azido-propyl)-7-phenyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a brown oil.

e) 0.64 g (2.04 mmol) of (S)-1-(2-azido-propyl)-7-phenyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol were hydrogenated on 65 mg of platinum oxide for 2 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The greenish solid obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 118 mg (1.02 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 15 hours and the beige crystals were subsequently filtered off. 0.37 g (53%) of (S)-2-(7-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 202-204° was obtained.

Example 15

a) A solution of 16 g (108 mmol) of 6-hydroxy-1-indanone, 22.3 ml (0.26 mol) of 3-buten-2-ol and 160 mg of p-toluene-sulphonic acid in 170 ml of 2,2-dimethoxy-propane was boiled under reflux for 38 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). In addition to 7.5 g of educt there were obtained 6.21 g (28%) of (RS)-2-(2-buten-1-yl)-6-hydroxy-1-indanone as a yellow oil.

b) A solution of 5.0 g (24.7 mmol) of (RS)-2-(2-buten-1-yl)-6-hydroxy-1-indanone, 4.1 ml (54.4 mmol) of ethyl bromide, 6.83 g (49.4 mmol) of potassium carbonate and 10 ml of N,N-dimethylformamide in 70 ml of acetone was heated to 35° for 35 hours. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. 5.6 g (98%) of (RS)-2-(2-buten-1-yl)-6-ethoxy-1-indanone were obtained as a red-brown oil which was used directly in the next reaction.

c) An ozone stream (3 g ozone/hour) was conducted for 90 minutes while stirring through a solution, cooled to -70°, of 5.6 g (24.3 mmol) of (RS)-2-(2-buten-1-yl)-6-ethoxy-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2.72 ml (37.1 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 170 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently

poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 3.4 g (64%) of (RS)-2-(2-oxoethyl)-6-ethoxy-1-indanone were obtained as a red-brown oil.

10 d) A solution of 1.6 g (7.33 mmol) of (RS)-2-(2-oxoethyl)-6-ethoxy-1-indanone and 70 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.2 g (29.3 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling
15 solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 4:1). 1.03 g (52%) of (R)-1-(7-ethoxy-1,4-
20 dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

e) 0.59 ml (7.6 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of
25 1.03 g (3.8 mmol) of (R)-1-(7-ethoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.1 ml (15.2 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane,
30 washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated
35 in a vacuum. The green oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 0.6 g (9.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 20 hours while stirring. After cooling the solution was poured into

100 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (ethyl acetate/hexane 1:10). 948 mg (72%) of (S)-1-(2-azido-propyl)-7-ethoxy-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a light yellowish oil.

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f) 0.94 g (3.32 mmol) of (S)-1-(2-azido-propyl)-7-ethoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 80 ml of anhydrous ethanol were hydrogenated on 94 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 198 mg (1.7 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 581 mg (56%) of (S)-2-(7-ethoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 212-214° were obtained.

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Example 16

a) A solution of 4.74 g (21.6 mmol) of (RS)-2-(2-buten-1-yl)-6-hydroxy-1-indanone, 5.18 ml (47.6 mmol) of isobutyl bromide and 5.98 g (43.3 mmol) of potassium carbonate in 40 ml of N,N-dimethylformamide was heated to 60° for 48 hours. After cooling the solution was poured into 100 ml of water and extracted twice with 70 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. 5.2 g (93%) of (RS)-2-(2-buten-1-yl)-6-isobutoxy-1-indanone were obtained as a red-brown oil which was used directly in the next reaction.

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b) An ozone stream (2 g ozone/hour) was conducted for 90 minutes while stirring through a solution, cooled to -70° , of 5.1 g (19.7 mmol) of (RS)-2-(2-buten-1-yl)-6-isobutoxy-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2.16 ml (29.4 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 170 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 2.3 g (48%) of (RS)-2-(2-oxoethyl)-6-isobutoxy-1-indanone were obtained as a red-brown oil.

c) A solution of 2.3 g (9.34 mmol) of (RS)-2-(2-oxoethyl)-6-isobutoxy-1-indanone and 70 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.93 g (37.3 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:4). 1.52 g (57%) of (RS)-1-(7-isobutoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a red oil.

d) 0.81 ml (10.5 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0° , of 1.5 g (5.26 mmol) of (RS)-1-(7-isobutoxy-1,4-dihydro-indeno[1,2-

b]pyrrol-1-yl)-propan-2-ol and 2.93 ml (21.0 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 0.68 g (10.5 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (ethyl acetate/hexane 1:4). 0.43 g (26%) of (RS)-1-(2-azido-propyl)-7-ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellowish oil.

e) 0.43 g (1.38 mmol) of (RS)-1-(2-azido-propyl)-7-isobutoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 50 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 80 mg (0.69 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 0.25 mg (53%) of (RS)-2-(7-isobutoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 178° were obtained.

Example 17

- a) A solution of 11.8 g (73.7 mmol) of 6-ethyl-1-indanone, 15.4 ml (0.18 mol) of 3-buten-2-ol and 110 mg of p-toluene-sulphonic acid in 110 ml of 2,2-dimethoxy-propane was boiled under reflux for 46 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 5:1). 7.92 g (50%) of (RS)-2-(2-buten-1-yl)-6-ethyl-1-indanone were obtained as a yellow oil.
- b) An ozone stream (3 g ozone/hour) was conducted for 40 minutes while stirring through a solution, cooled to -70°, of 7.92 g (37.0 mmol) of (RS)-2-(2-buten-1-yl)-6-ethyl-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 3.36 ml (45.8 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 150 ml of dichloromethane and, after the addition of 30 ml of water and 30 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 6.94 g (93%) of (RS)-2-(2-oxoethyl)-6-ethyl-indanone were obtained as a yellow oil.
- c) A solution of 2.02 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-ethyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution

over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1).
5 1.7 g (71%) of (R)-1-(7-ethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.1 ml (14.1 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.7 g
10 (7.04 mmol) of (R)-1-(7-ethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.9 ml (28.2 mmol) of triethylamine in 55 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed
15 twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated
20 in a vacuum. The green oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.84 g (12.8 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 120 ml of water and extracted twice with 120 ml of ethyl
25 acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene).
30 0.74 g (40%) of (S)-1-(2-azido-propyl)-7-ethyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a yellow oil.

e) 0.74 g (2.7 mmol) of (S)-1-(2-azido-propyl)-7-ethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous
35 ethanol were hydrogenated on 80 mg of platinum oxide for 15 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 50 ml of anhydrous

diethyl ether, filtered and treated while stirring with a solution of 345 mg (2.97 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 0.45 g (56%) of (S)-2-(7-ethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 189-190° was obtained.

Example 18

- 10 a) A solution of 8 g (42 mmol) of 6-methoxycarbonyl-1-indanone, 8 ml (0.1 mol) of 3-buten-2-ol and 100 mg of p-toluenesulphonic acid in 80 ml of 2,2-dimethoxy-propane was boiled under reflux for 28 hours on a water separator filled with
15 molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 3:1). In addition to 1.3 g of educt there were obtained 8.5 g (83%) of (RS)-2-(2-buten-1-yl)-6-methoxycarbonyl-1-indanone
20 as a yellow oil.
- b) An ozone stream (3 g ozone/hour) was conducted for 45 minutes while stirring through a solution, cooled to -70°, of 10.5 g (42.9 mmol) of (RS)-2-(2-buten-1-yl)-6-methoxycarbonyl-1-indanone in 150 ml of anhydrous dichloromethane.
25 Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.74 ml (64.4 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 18 hours. The reaction mixture was
30 evaporated in a vacuum and purified by column chromatography on silica gel (diethyl ether). By recrystallization of the resulting solid there were obtained 4.5 g (45%) of (RS)-2-(2-oxoethyl)-6-methoxycarbonyl-1-indanone as a light yellow solid with m.p. 92°.
- 35 c) A solution of 2.32 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-methoxycarbonyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3 g (40 mmol) of (RS)-1-amino-2-

propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 2.2 g (81%) of (RS)-1-(7-methoxycarbonyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.26 ml (16.2 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.2 g (8.1 mmol) of (RS)-1-(7-methoxycarbonyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 4.55 ml (32.4 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 1.05 g (16.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 950 mg (40%) of (RS)-1-(2-azido-propyl)-7-methoxycarbonyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a light brown oil.

e) 0.95 g (3.2 mmol) of (RS)-1-(2-azido-propyl)-7-methoxycarbonyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 70 ml of anhydrous methanol were hydrogenated on 95 mg of platinum

oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with methanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 110 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution
5 of 186 mg (1.6 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 3 hours and the white crystals were subsequently filtered off. 770 mg (73%) of (RS)-2-(7-methoxycarbonyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 199-200°
10 were obtained.

Example 19

a) A 2M phenyllithium solution was added dropwise over
15 5 minutes to a solution, cooled to 0°, of 3.55 g (10.7 mmol) of (RS)-1-(2-azido-propyl)-7-mesyloxy carbonyl-1,4-dihydro-indeno[1,2-b]pyrrole, 90 ml of anhydrous diethyl ether and 90 ml of anhydrous tetrahydrofuran. After 15 minutes at this temperature a further 5.87 ml of the phenyllithium solution were added
20 dropwise and the mixture was stirred for a further 5 minutes. Subsequently, the reaction mixture was treated with 50 ml of a saturated ammonium chloride solution and 25 ml of water. The mixture was extracted once with 50 ml of ethyl acetate and the aqueous phase was made slightly acidic with 1N hydrochloric acid
25 and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. 2.7 g (99%) of (RS)-1-(2-azido-propyl)-7-hydroxy-1,4-dihydro-indeno[1,2-b]-
30 pyrrole were obtained as a brown oil.

b) 0.7 ml (7.4 mmol) of acetic anhydride was added while stirring to a solution of 1.05 g (4.13 mmol) of (RS)-1-(2-azido-propyl)-7-hydroxy-1,4-dihydro-indeno[1,2-b]pyrrol and 0.6 ml
35 (7.4 mmol) of pyridine in 30 ml of dichloromethane and the mixture was stirred for a further 16 hours. Subsequently, the reaction mixture was treated with 50 ml of dichloromethane and 40 ml of water, the organic phase was separated and this was

washed once with 50 ml of saturated sodium chloride solution. After drying over magnesium sulphate the solution was concentrated in a vacuum and the crude product was purified by column chromatography on silica gel (ethyl acetate/hexane 1:2). 0.9 g (85%) of (RS)-1-(2-azido-propyl)-7-acetoxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light orange oil.

c) 0.84 g (2.84 mmol) of (RS)-1-(2-azido-propyl)-7-acetoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol was hydrogenated on 85 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 178 mg (1.54 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 4 hours and the white crystals were subsequently filtered off. 400 mg (43%) of (RS)-2-(7-acetoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 187-188° were obtained.

Example 20

a) A solution of 1.88 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-methyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 0.99 g (44%) of (RS)-1-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

b) 0.67 ml (8.6 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of

- 0.98 g (4.3 mmol) of (RS)-1-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.4 ml (17.2 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture
5 was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated
10 sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.56 g (8.6 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was
15 poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The
20 brown oil obtained was purified by column chromatography on silica gel (toluene). 737 mg (68%) of (RS)-1-(2-azido-propyl)-7-methyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a colourless oil.
- 25 c) 0.73 g (2.89 mmol) of (RS)-1-(2-azido-propyl)-7-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 40 ml of anhydrous ethanol were hydrogenated on 75 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colour-
30 less oil obtained was dissolved in 50 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 168 mg (1.45 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 596 mg (73%) of
35 (RS)-2-(7-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 194° were obtained.

Example 21

a) A solution of 2.08 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-chloro-1-indanone and 80 mg of p-toluenesulphonic acid in
5 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent
10 was reduced to a volume of 30 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 3:7). 1.52 g (61%) of (RS)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil which was used directly in the next reaction.

15

b) 0.95 ml (12.3 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°C, of 1.52 g (6.1 mmol) of (RS)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.4 ml (24.5 mmol) of triethyl-
20 amine in 40 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 280 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were washed
25 once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 718 mg (11.0 mmol) of sodium
30 azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time and once with 140 ml of ethyl acetate. The combined organic phases were washed once with 140 ml of water
35 and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.0 g (60%) of (RS)-1-(2-

azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]-pyrrole was obtained as an oil.

c) 1.0 g (3.7 mmol) of (RS)-1-(2-azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]-pyrrole dissolved in 40 ml of anhydrous ethanol was hydrogenated on 100 mg of platinum oxide for 17 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 75 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 195 mg (1.68 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 19 hours and the white crystals were subsequently filtered off. 945 mg (85%) of (RS)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 206° were obtained.

Example 22

a) A solution of 2 g (9.8 mmol) of (RS)-2-(2-oxoethyl)-6-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.94 g (39.2 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 1.7 g (71%) of (RS)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a solid with m.p. 76°.

b) 0.64 ml (8.2 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°C, of 1 g (4.1 mmol) of (RS)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-propan-2-ol and 2.3 ml (16.4 mmol) of triethylamine in 30 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed

twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.53 g (8.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 750 mg (68%) of (RS)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole as a colourless oil.

c) 1 g (3.7 mmol) of (RS)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 100 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 216 mg (1.8 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 882 mg (79%) of (RS)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 203° were obtained.

Example 23

a) A solution of 20.0 g (0.12 mol) of 6-methoxy-1-indanone, 31.3 ml (0.36 mol) of 3-buten-2-ol, 53.5 ml (0.43 mol) of 2,2-dimethoxypropane and 200 mg of p-toluenesulphonic acid in 200 ml of toluene was brought to boiling. The resulting methanol/acetone mixture was distilled off and the reaction

solution was subsequently boiled under reflux overnight. After cooling the solution was washed with 50 ml of saturated sodium hydrogen carbonate solution. The aqueous washing was extracted with 50 ml of ethyl acetate, the organic phases were combined,
5 dried with magnesium sulphate and evaporated in a vacuum.

Purification on silica gel (hexane/diethyl ether 5:1) yielded 13.6 g (55%) of (RS)-2-(2-buten-1-yl)-6-methoxy-1-indanone as a pale yellow oil.

- 10 b) Ozone (3 g ozone/hour) was conducted for 60 minutes while stirring through a solution, cooled to -70° , of 13.6 g (62 mmol) of (RS)-2-(2-buten-1-yl)-6-methoxy-1-indanone in 200 ml of anhydrous dichloromethane and 400 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen and then
15 6.4 ml (87 mmol) of dimethyl sulphide were added to the cold solution. The solution came to room temperature overnight and was evaporated in a vacuum. The residue was dissolved in 1600 ml of dichloromethane, the solution was treated with 600 g of silica gel and 100 ml of 10% oxalic acid solution and
20 stirred overnight. Then, the mixture was filtered and the filtrate was concentrated in a vacuum. 6.5 g (51%) of (RS)-2-(2-oxoethyl)-6-methoxy-1-indanone were obtained as a yellow oil.

- c) A solution of 4.5 g (22 mmol) of (RS)-2-(2-oxoethyl)-6-
25 methoxy-1-indanone and 2.3 g (22 mmol) of N-acetylene-diamine in 100 ml of toluene was boiled under reflux for 10 minutes. The reaction mixture was evaporated in a vacuum, taken up in dichloromethane, dried with magnesium sulphate and again evaporated. After purification on silica gel (ethyl acetate) 0.9 g
30 (15%) of N-[2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethyl]-acetamide was obtained as a yellowish solid.

- d) 2.4 g (8.9 mmol) of N-[2-(7-methoxy-1,4-dihydro-indeno-
[1,2-b]pyrrol-1-yl)-ethyl]-acetamide were heated to 140° for 17
35 hours under argon in 48 ml of ethylene glycol/water 2:1 in the presence of 2.5 g of potassium hydroxide. The mixture was left to cool and treated with 250 ml of semi-saturated sodium chloride solution. The mixture was extracted three times with

diethyl ether and the combined extracts were dried over sodium sulphate, filtered and evaporated. The brown oil was dissolved in 30 ml of methanol and treated with 1.0 g (8.6 mmol) of fumaric acid, following which pale brown crystals separated. These were
5 dissolved in 120 ml of warm methanol. After cooling to room temperature the product was crystallized out by the slow addition of 120 ml of diethyl ether. 2.0 g (66%) of 2-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:1) with m.p. 177-180° were obtained.

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Example 24

a) A solution of 2.0 g (10.4 mmol) of (RS)-2-(2-oxoethyl)-5-fluoro-1-indanone and 85 mg of p-toluenesulphonic acid in
15 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.12 g (41.6 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent
20 was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.66 g (69%) of (RS)-1-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

25

b) 1.12 ml (14.3 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.66 g (7.17 mmol) of (RS)-1-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.98 ml (28.7 mmol) of triethyl-
30 amine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 70 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were
35 extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of

anhydrous dimethylformamide, treated with 0.82 g (12.5 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 80 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.45 g (24%) of (RS)-1-(2-azido-propyl)-6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a yellow oil.

c) 0.44 g (1.71 mmol) of (RS)-1-(2-azido-propyl)-6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol were hydrogenated on 45 mg of platinum oxide for 5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 40 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 100 mg (0.86 mmol) of fumaric acid in 7 ml of methanol. The mixture was stirred at room temperature for 15 hours and the white crystals were subsequently filtered off. 0.39 g (80%) of (RS)-2-(6-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 202° was obtained.

Example 25

a) A solution of 10.6 g (63.3 mmol) of 5,6-difluoro-1-indanone, 13.1 ml (0.15 mol) of 3-buten-2-ol and 110 mg of p-toluenesulphonic acid in 110 ml of 2,2-dimethoxy-propane was boiled under reflux for 64 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 2:1). In addition to 3.6 g of educt there were obtained 5.32 g (38%) of (RS)-2-(2-buten-1-yl)-5,6-difluoro-1-indanone as a brown oil.

b) An ozone stream (2 g ozone/hour) was conducted for 40 minutes while stirring through a solution, cooled to -70° , of 5.3 g (23.8 mmol) of (RS)-2-(2-buten-1-yl)-5,6-difluoro-1-indanone in 125 ml of anhydrous dichloromethane and 25 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2.64 ml (36 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 60 ml of dichloromethane and, after the addition of 10 ml of water and 10 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 80 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 40 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There was obtained a yellow oil which was crystallized from diethyl ether/hexane. 3.82 g (76%) of (RS)-2-(2-oxoethyl)-5,6-difluoro-1-indanone were obtained as a white solid with m.p. $78-81^{\circ}$.

c) A solution of 2.1 g (10 mmol) of (RS)-2-(2-oxoethyl)-5,6-difluoro-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.13 g (45%) of (R)-1-(6,7-difluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown solid which was used without further recrystallization in the next reaction.

d) 0.7 ml (9 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0° , of 1.13 g

- (4.5 mmol) of (R)-1-(6,7-difluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.48 ml (18 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 70 ml of dichloromethane, washed twice with 60 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 60 ml of dichloromethane. The combined organic phases were washed with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.58 g (8.98 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted three times with 70 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 0.97 g (79%) of (S)-1-(2-azido-propyl)-6,7-difluoro-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.
- e) 0.97 g (3.5 mmol) of (S)-1-(2-azido-propyl)-6,7-difluoro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 100 mg of platinum oxide for 18 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 75 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 406 mg (3.5 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 22 hours and the white crystals were subsequently filtered off. 0.78 g (61%) of (S)-2-(6,7-difluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 215-217° was obtained.

Example 26

- a) A solution of 14.5 g (64.5 mmol) of 5-chloro-6-methoxy-3,3-dimethyl-1-indanone, 13.3 ml (0.15 mol) of 3-buten-2-ol and 300 mg of p-toluenesulphonic acid in 150 ml of 2,2-dimethoxy-propane was boiled under reflux for 71 hours on a water separator filled with molecular sieve (0.4 nm 2 mm, pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 6:1). In addition to 2.25 g of educt there were obtained 11.9 g (66%) of (RS)-2-(2-buten-1-yl)-5-chloro-6-methoxy-3,3-dimethyl-1-indanone as a pale yellow solid with m.p. 86°.
- b) An ozone stream (3 g ozone/hour) was conducted for 50 minutes while stirring through a solution, cooled to -70°, of 11.9 g (42.7 mmol) of (RS)-2-(2-buten-1-yl)-5-chloro-6-methoxy-3,3-dimethyl-1-indanone in 160 ml of anhydrous dichloromethane and 40 ml of anhydrous methanol. Subsequently, the mixture was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.7 ml (64 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 120 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. The oil obtained was crystallized from hexane/ethyl acetate. 10.3 g (90%) of (RS)-2-(2-oxoethyl)-5-chloro-6-methoxy-3,3-dimethyl-1-indanone were obtained as a light yellow solid with m.p. 102-103°.

c) A solution of 6.67 g (25 mmol) of (RS)-2-(2-oxoethyl)-5-chloro-6-methoxy-3,3-dimethyl-1-indanone and 150 mg of p-toluenesulphonic acid in 200 ml of anhydrous toluene was heated on a water separator. A solution of 7.51 g (0.1 mol) of (R)-1-amino-2-propanol in 40 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 40 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:1). 7.0 g (92%) of (R)-1-(6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 0.93 ml (12 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.84 g (6.0 mmol) of (R)-1-(6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.35 ml (24 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloromethane, washed twice with 90 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.78 g (12 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 3:1). 1.58 g (80%) of (S)-1-(2-azido-propyl)-6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a red oil.

e) 1.56 g (4.72 mmol) of (S)-1-(2-azido-propyl)-6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 5 160 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The light yellow oil obtained was dissolved in 125 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 548 mg (4.72 mmol) of 10 fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 19 hours and the white crystals were subsequently filtered off. 1.57 g (80%) of (S)-2-(6-chloro-7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 186-188° were 15 obtained.

Example 27

a) A solution of 1.92 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-fluoro-1-indanone and 80 mg of p-toluenesulphonic acid in 20 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (S)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled 25 for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.51 g (65%) of (S)-1-(7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

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b) 0.51 ml (13.1 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.51 g (6.5 mmol) of (S)-1-(7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.64 ml (26.1 mmol) of triethyl- 35 amine in 40 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 60 ml of saturated sodium hydrogen carbonate sol-

ution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum.

- 5 The brown oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 711 mg (10.9 mmol) of sodium azide and the reaction mixture was heated to 50° for 16 hours while stirring. After cooling the solution was poured into 110 ml of water and extracted twice with 110 ml of ethyl acetate each time. The combined organic phases were washed once
10 with 90 ml of water and once with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 631 mg
15 (38%) of (R)-1-(2-azido-propyl)-7-fluoro-1,4-dihydro-indeno-[1,2-b]pyrrole were obtained as an oil.

- c) 620 mg (2.4 mmol) of (R)-1-(2-azido-propyl)-7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous
20 ethanol were hydrogenated on 62 mg of platinum oxide for 15 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 75 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of
25 140 mg (1.2 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 4.5 hours and the white crystals were subsequently filtered off. 409 mg (53%) of (R)-2-(7-fluoro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 174° were obtained.

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Example 28

- a) A solution of 2 g (9.8 mmol) of (RS)-2-(2-oxoethyl)-6-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in
35 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.94 g (39.2 mmol) of (S)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture

was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 1.5 g (63%) of (S)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a solid with m.p. 74°.

b) 0.96 ml (12.3 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.5 g (6.2 mmol) of (S)-1-(7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.45 ml (24.6 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 60 ml of anhydrous dimethylformamide, treated with 0.71 g (10.9 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.0 g (60%) of (R)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

c) 1 g (3.7 mmol) of (R)-1-(2-azido-propyl)-7-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 100 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl

ether, filtered and treated while stirring with a solution of 240 mg (2.07 mmol) of fumaric acid dissolved in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off.
5 760 mg (68%) of (R)-2-(7-methoxy-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 207° were obtained

Example 29

10 a) A solution of 2.5 g (12.0 mmol) of (RS)-2-(2-oxoethyl)-6-chloro-1-indanone and 100 mg of p-toluenesulphonic acid in 120 ml in anhydrous toluene was heated on a water separator. A solution of 3.6 g (47.9 mmol) of (S)-1-amino-2-propanol in
15 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl
20 acetate/toluene 1:1). 1.56 g (53%) of (S)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil which was used directly in the next reaction.

(b) 0.97 ml (12.5 mmol) of methanesulphonyl chloride was
25 added dropwise while stirring to a solution, cooled to 0°, of 1.55 g (6.3 mmol) of (S)-1-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.5 ml (25.0 mmol) of triethyl-amine in 40 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture
30 was subsequently diluted with 200 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed to 70 ml of saturated
35 sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 815 mg (12.5 mmol) of sodium azide and the reaction mixture was heated

to 60° for 17 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of ethyl acetate each time. The combined organic phases were washed once with 140 ml of water and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 833-mg (49%) of (R)-1-(2-azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as an oil.

c) 750 mg (2.8 mmol) of (R)-1-(2-azido-propyl)-7-chloro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol were hydrogenated on 75 mg of platinum oxide for 16 hours. Subsequently, the catalyst was filtered off under suction, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 154 mg (1.3 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 6 hours and the white crystals were subsequently filtered off. 633 mg (76%) of (R)-2-(7-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 195° were obtained.

Example 30

a) A solution of 3 g (13.9 mmol) of (RS)-2-(2-oxoethyl)-7-methoxy-1-tetralone and 150 mg of p-toluenesulphonic acid in 130 ml in anhydrous toluene was heated on a water separator. A solution of 4.16 g (55.5 mmol) of (S)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). 3.0 g (84%) of (S)-1-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-propan-2-ol were obtained as a brown oil which was used directly in the next reaction.

(b) 1.8 ml (23.3 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 3 g (11.7 mmol) of (S)-1-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)propan-2-ol and 6.55 ml (46.7 mmol) of triethylamine in 80 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 300 ml of diethyl ether, washed twice with 100 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 100 ml of diethyl ether. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The oil obtained was dissolved in 70 ml of anhydrous dimethylformamide, treated with 1.52 g (23.3 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.9 g (58%) of (R)-1-(2-azido-propyl)-4,5-dihydro-8-methoxy-1H-benz[g]indole were obtained as a light yellow oil.

c) 1.9 g (6.4 mmol) of (R)-1-(2-azido-propyl)-4,5-dihydro-8-methoxy-1H-benz[g]indole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 190 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. There were obtained 1.64 g (95%) of (R)-2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine as a colourless oil, of which 440 mg (1.7 mmol) were dissolved in 70 ml of anhydrous ether, filtered and treated while stirring with a solution of 200 mg (1.7 mmol) of fumaric acid in 20 ml of methanol the mixture was stirred at room temperature for 2 hours and the white crystals were subsequently filtered off. 450 mg (70%) of

(R)-2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 194° were obtained.

Example 31

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a) A solution of 1.2 g (4.7 mmol) of (R)-2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine, 0.52 g (5.1 mmol) of triethylamine and 0.83 g (5.8 mmol) of ethyl trifluoroacetate in 50 ml of anhydrous methanol was stirred at
10 room temperature for 27 hours. After the solvent had been drawn off in a vacuum the residue was taken up with 70 ml of anhydrous dioxan, 1.8 g (7.9 mmol) of DDQ were added and the mixture was boiled under reflux for 1.5 hours. Subsequently, the reaction mixture was concentrated in a vacuum and the residue
15 was purified by column chromatography on silica gel (dichloromethane/acetone 4:1). 0.97 g (59%) of (R)-N-[2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethyl]-trifluoroacetamide was obtained as a pale brown solid which was used in the next reaction without further recrystallization.

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b) A mixture of 0.97 g (2.8 mmol) of (R)-N-[2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethyl]-trifluoroacetamide, 1 g (17.8 mmol) of potassium hydroxide, 2 ml of water and 40 ml of methanol was boiled under reflux for 15 hours. The reaction
25 mixture was subsequently poured into 80 ml of 1N sodium hydroxide solution, extracted twice with 80 ml of diethyl ether each time and once with 80 ml of ethyl acetate and the combined organic phases were washed once with 120 ml and dried over magnesium sulphate. After concentration in a vacuum the residue
30 was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 322 mg (2.77 mmol) of fumaric acid in 30 ml of methanol. The mixture was stirred at room temperature for 3 hours and the white crystals were subsequently filtered off. 600 mg (69%) of (R)-2-(8-methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with
35 m.p. 209° were obtained.

Example 32

a) 254 mg (1.0 mmol) of N-[2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were dissolved in 10 ml of dioxan under argon, 238 mg (1.05 mmol) of DDQ were added and the mixture was heated to reflux for 1 hr. Separated crystals were removed by filtration, the filtrate was evaporated and the residue was chromatographed on 50 g of silica gel with methylene chloride/acetone 9:1. 211 mg (83%) of N-[2-(8-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were obtained as a light yellowish solid. Tlc (silica gel): R_f = 0.25 (methylene chloride/acetone 9:1).

b) 211 mg (0.83 mmol) of N-[2-(8-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 9.5 hr. under argon in 3 ml of ethylene glycol/water 2:1 in the presence of 0.25 g (4.4 mmol) of potassium hydroxide. The reaction mixture was left to cool and was poured into 20 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether and the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 2 ml of methanol and 70 mg (0.6 mmol) of fumaric acid were added. After the addition of 5 ml of diethyl ether the crystals were filtered off and recrystallized from 8.5 ml of methanol/DMF 16:1. 142 mg (53%) of 2-(8-methoxy-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) were obtained as white crystals with m.p. 200-201°.

Example 33

a) A solution of 20 g (104 mmol) of 5,6-dimethoxy-1-indanone, 21.5 ml (0.25 mol) of 3-buten-2-ol and 200 mg of p-toluenesulphonic acid in 21.5 ml of 2,2-dimethoxypropane and 200 ml of anhydrous toluene was boiled under reflux for 24 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel

(hexane/ethyl acetate 3:2). 6.8 g (27%) of (RS)-2-(2-buten-1-yl)-5,6-dimethoxy-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted while stirring for 30 minutes through a solution, cooled to -70° , of 6.8 g (27.6 mmol) of (RS)-2-(2-buten-1-yl)-5,6-dimethoxy-1-indanone in 100 ml of anhydrous dichloromethane and 20 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4 ml (54.3 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 250 ml of dichloromethane and, after the addition of 10 ml of water and 10 ml of trifluoroacetic acid, stirred at room temperature for 1.5 hours. The mixture was subsequently poured into 100 ml of water and neutralized while stirring by the spatula-wise addition of sodium hydrogen carbonate. A further 70 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 120 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was crystallized from diethyl ether/hexane. 4.7 g (73%) of (RS)-2-(2-oxoethyl)-5,6-dimethoxy-1-indanone were obtained as a light yellow solid with m.p. 122° .

c) A solution of 2 g (8.5 mmol) of (RS)-2-(2-oxoethyl)-5,6-dimethoxy-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.56 g (34.2 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 0.91 g (40%) of (RS)-1-(1,4-dihydro-6,7-dimethoxy-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol was obtained as an oil.

d) 0.52 ml (6.7 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.91 g (3.3 mmol) of (RS)-1-(1,4-dihydro-6,7-dimethoxy-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 1.86 ml (13.4 mmol) of triethylamine in 25 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 140 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.43 g (6.7 mmol) of sodium azide and the reaction mixture was heated to 60° for 15 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene/ethyl acetate 4:1). 400 mg (40%) of (RS)-1-(2-azido-propyl)-1,4-dihydro-6,7-dimethoxy-indeno[1,2-b]-pyrrole were obtained as an oil which was used in the next reaction without further purification.

e) 0.4 g (1.3 mmol) of (RS)-1-(2-azido-propyl)-1,4-dihydro-6,7-dimethoxy-indeno[1,2-b]pyrrole dissolved in 20 ml of anhydrous ethanol was hydrogenated on 40 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 25 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 62.2 mg (0.54 mmol) of fumaric acid in 5 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 314 mg (71%) of

(RS)-2-(1,4-dihydro-6,7-dimethoxy-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate with m.p. 203-205° were obtained.

Example 34

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a) A solution of 48 g (0.324 mol) of 4-chromanone, 67 ml (0.78 mol) of 3-buten-2-ol and 500 mg of p-toluenesulphonic acid in 67 ml of 2,2-dimethoxypropane and 500 ml of anhydrous toluene was boiled under reflux for 46 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 24.7 g (38%) of (RS)-2-(2-buten-1-yl)-4-chromanone were obtained as a yellow oil.

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b) An ozone stream (3.5 g ozone/hour) was conducted while stirring for 2 hours through a solution, cooled to -70°, of 24.6 g (0.12 mol) of (RS)-2-(2-buten-1-yl)-4-chromanone in 450 ml of anhydrous dichloromethane and 150 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 15 minutes. After the addition of 13.4 ml (0.18 mol) of dimethyl sulphide the mixture was stirred at room temperature for 20 hours. The reaction mixture was subsequently evaporated in a vacuum, the residue was treated with 250 ml of dichloromethane and, after the addition of 40 ml of water and 40 ml of trifluoroacetic acid, stirred at room temperature for 4 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 70 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 120 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 22.7 g (99%) of 2-(2-oxoethyl)-4-chromanone were obtained as a yellow oil which was used in the next reaction without further purification.

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c) A solution of 1.9 g (10 mmol) of (RS)-2-(2-oxoethyl)-4-chromanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of

3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.82 g (79%) of (RS)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol were obtained as a yellow oil.

d) 1.23 ml (15.9 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.82 g (7.9 mmol) of (RS)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol and 4.4 ml (31.7 mmol) of triethylamine in 50 ml of anhydrous dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 280 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide treated with 1.03 g (15.9 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.44 g (71%) of (RS)-1-(2-azido-propyl)-1,4-dihydro-[1]benzopyrano[4,3-b]pyrrole were obtained as a colourless oil.

e) 1.44 g (5.7 mmol) of (RS)-1-(2-azido-propyl)-1,4-dihydro-[1]benzopyrano[4,3-b]pyrrole dissolved in 60 ml of anhydrous ethanol were hydrogenated on 150 mg of platinum oxide for

4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of
5 329 mg (2.83 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 1.42 g (88%) of (RS)-1-(1,4-dihydro-[1]benzopyrano-[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 208-209° were
10 obtained.

Example 35

a) A lithium diisopropylamide solution, freshly prepared from
15 3.12 ml (22 mmol) of diisopropylamine and 13.8 ml (22 mmol) of 1.6N n-butyllithium in hexane, in 40 ml of anhydrous tetrahydrofuran was added dropwise while stirring to a solution, cooled to -70°, of 2.96 g (18.3 mmol) of 6-methoxy-1-indanone in 300 ml of anhydrous tetrahydrofuran. The mixture was stirred
20 at this temperature for a further 30 minutes and a solution of 2.03 ml (20.2 mmol) of 3-chloro-2-butenone dissolved in 40 ml of anhydrous tetrahydrofuran was subsequently added dropwise over 10 minutes. The reaction mixture was left to come to room temperature over 30 minutes and was stirred at this temp-
25 erature for a further 30 minutes. Subsequently, the reaction mixture was poured on to 150 ml of ice, 150 ml of saturated sodium chloride were added and the organic phase was separated. The aqueous phase was extracted once with 400 ml of diethyl ether, the combined organic phases were washed once with
30 200 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The red oil obtained was purified by column chromatography on silica gel (hexane/diethyl ether 3:2). In addition to 0.93 g of educt there were obtained 1.56 g (37%) of rac-6-methoxy-2-(3-oxo-2-butyl)-1-indanone as a yellow oil.
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b) A solution of 1.5 g (6.46 mmol) of rac-6-methoxy-2-(3-oxo-2-butyl)-1-indanone and 80 mg of p-toluenesulphonic acid in

70 ml of anhydrous toluene was heated on a water separator. A solution of 1.94 g (25.8 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture
5 was boiled for a further 85 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.23 g (70%) of (R)-1-(7-methoxy-2,3-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol
10 were obtained as a yellow oil.

c) 0.7 ml (9.0 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.22 g (4.5 mmol) of (R)-1-(7-methoxy-2,3-dimethyl-1,4-dihydro-
15 indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.5 ml (18 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 60 ml of saturated sodium hydrogen
20 carbonate solution each time and the combined aqueous phases were extracted once with 60 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in
25 40 ml of anhydrous dimethylformamide, treated with 0.58 g (9.0 mmol) of sodium azide and the reaction mixture was heated to 80° for 18 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice times with
100 ml of ethyl acetate each time. The combined organic phases
30 were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.64 g (48%) of (S)-1-(2-azido-propyl)-7-methoxy-2,3-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole
35 were obtained as a light yellow oil.

d) 0.63 g (2.12 mmol) of (S)-1-(2-azido-propyl)-7-methoxy-2,3-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 40 ml of anhydrous ethanol were hydrogenated on 63 mg of platinum oxide for 2.5 hours. The catalyst was subsequently
5 filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 50 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 123 mg (1.06 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 16
10 hours and the light yellow crystals were subsequently filtered off. 528 mg (76) of (S)-2-(7-methoxy-2,3-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:05) with m.p. 197° were obtained.

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Example 36

a) A lithium diisopropylamide solution, freshly prepared from 3.12 ml (22 mmol) of diisopropylamine and 13.8 ml (22 mmol) of 1.6N n-butyllithium in hexane, in 40 ml of anhydrous tetra-
20 hydrofuran was added dropwise while stirring to a solution, cooled to -70°, of 2.96 g (18.3 mmol) of 6-methoxy-1-indanone in 300 ml of anhydrous tetrahydrofuran. The mixture was stirred at this temperature for a further 30 minutes and a solution of 1.62 ml (20.2 mmol) of chloroacetone dissolved in 40 ml of
25 anhydrous tetrahydrofuran was subsequently added dropwise over 10 minutes. The reaction mixture was left to come to room temperature over 90 minutes and was stirred at this temperature for a further 45 minutes. Subsequently, the reaction mixture was poured on to 100 ml of ice, 100 ml of saturated
30 sodium chloride were added and the organic phase was separated. The aqueous phase was extracted once with 300 ml of diethyl ether, the combined organic phases were washed once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The red oil
35 obtained was purified by column chromatography on silica gel (hexane/diethyl ether 3:2). There were obtained 2.24 g (56%) of (RS)-6-methoxy-2-(2-oxopropyl)-1-indanone as a yellow solid

which was used without further recrystallization in the next reaction.

b) A solution of 1.45 g (6.64 mmol) of (RS)-6-methoxy-2-(2-oxopropyl)-1-indanone and 60 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.0 g (26.6 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 90 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.05 g (61%) of (R)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a yellow solid with m.p. 110°.

c) 0.48 ml (6.2 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.8 g (3.1 mmol) of (R)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 1.73 ml (12.4 mmol) of triethylamine in 40 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 60 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 25 ml of anhydrous dimethylformamide, treated with 0.40 g (6.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on

silica gel (toluene). 0.44 g (50%) of (S)-1-(2-azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellow oil.

- 5 d) 0.44 g (1.56 mmol) of (S)-1-(2-azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 35 ml of anhydrous ethanol was hydrogenated on 45 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The
10 light yellow oil obtained was dissolved in 35 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 90 mg (0.78 mmol) of fumaric acid in 7 ml of methanol. The mixture was stirred at room temperature for 18 hours and the light yellow crystals were subsequently filtered off. 414 mg
15 (84%) of (S)-2-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 199° were obtained.

Example 37

- 20 a) A solution of 14.0 g (84 mmol) of 4-chloro-1-indanone, 17.3 ml (0.20 mol) of 3-buten-2-ol and 140 mg of p-toluene-sulphonic acid in 140 ml of 2,2-dimethoxy-propane was boiled under reflux for 64 hours on a water separator filled with
25 molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 6:1). 15.2 g (81%) of (RS)-2-(2-buten-1-yl)-4-chloro-1-indanone were obtained as a yellow oil.

- 30 b) An ozone stream (3 g ozone/hour) was conducted for 90 minutes while stirring through a solution, cooled to -70°, of 15.1 g (68.4 mmol) of (RS)-2-(2-buten-1-yl)-4-chloro-1-indanone in 200 ml of anhydrous dichloromethane and 40 ml of
35 anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 7.55 ml (103 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 20 hours. The reaction

mixture was evaporated in a vacuum, the residue was treated with 200 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured
5 into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 120 ml of dichloromethane each time. The combined organic phases were dried over
10 magnesium sulphate and concentrated in a vacuum. 13.9 g (97%) of (RS)-2-(2-oxoethyl)-4-chloro-1-indanone were obtained as a light yellow oil.

c) A solution of 2.08 g (10.0 mmol) of (RS)-2-(2-oxoethyl)-
15 4-chloro-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture
20 was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:2). 1.47 g (59%) of (RS)-1-(5-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as
25 a brown oil.

d) 0.92 ml (11.9 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.47 g (5.93 mmol) of (RS)-1-(5-chloro-1,4-dihydro-indeno-
30 [1,2-b]pyrrol-1-yl)-propan-2-ol and 3.3 ml (23.7 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 50 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen
35 carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and

evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.77 g (11.9 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was
5 poured into 80 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The
10 brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 1.0 g (62%) of (RS)-1-(2-azido-propyl)-5-chloro-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellow oil.

15 e) 1.0 g (3.66 mmol) of (RS)-1-(2-azido-propyl)-5-chloro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 100 mg of platinum oxide for 5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colour-
20 less oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 212 mg (1.83 mmol) of fumaric acid in 16 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 1.05 g (94%) of
25 (RS)-2-(5-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 182° were obtained.

Example 38

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a) A solution of 1.8 g (8.25 mmol) of (RS)-6-methoxy-2-(2-oxoethyl)-1-indanone and 70 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.48 g (33 mmol) of (RS)-1-amino-2-propanol in
35 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 90 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture

was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.37 g (65%) of (RS)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown solid which was used directly in the next
5 reaction.

b) 0.81 ml (10.5 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.35 g (5.25 mmol) of (RS)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.92 ml
10 (21.0 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 120 ml of dichloromethane, washed twice with 70 ml of
15 saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil
20 obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.68 g (10.5 mmol) of sodium azide and the reaction mixture was heated to 80° for 23 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The
25 combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.93 g (63%) of (RS)-1-(2-
30 azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]-pyrrole was obtained as a light yellow oil.

c) 0.92 g (3.26 mmol) of (RS)-1-(2-azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in
35 70 ml of anhydrous ethanol was hydrogenated on 90 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The light yellow oil obtained was dissolved in 70 ml

of anhydrous diethyl ether, filtered and treated while stirring with a solution of 189 mg (1.63 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 18 hours and the light yellow crystals were subsequently filtered off. 800 mg (78%) of (RS)-2-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 187-188° were obtained.

Example 39

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a) A solution of 11.2 g (64.1 mmol) of 6-isopropyl-1-indanone, 13.3 ml (0.15 mol) of 3-buten-2-ol and 110 mg of p-toluenesulphonic acid, 10 ml of 2,2-dimethoxy-propane was boiled under reflux for 1 hours on a water separator filled with molecular sieve (0.4 mm 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 5:1). In addition to 6.6 g of educt there were obtained 5.6 g (38%) of (RS)-2-(2-buten-1-yl)-6-isopropyl-1-indanone as a yellow oil.

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b) An ozone stream (2 g ozone/hour) was conducted for 50 minutes while stirring through a solution, cooled to -70°, of 5.6 g (24.5 mmol) of (RS)-2-(2-buten-1-yl)-6-isopropyl-1-indanone in 125 ml of anhydrous dichloromethane and 25 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2.7 ml (36.8 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 60 ml of dichloromethane and, after the addition of 10 ml of water and 10 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 50 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloromethane each time. The combined organic phases were dried over magnesium

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sulphate and concentrated in a vacuum. 5.08 g (95%) of (RS)-2-(2-oxoethyl)-6-isopropyl-1-indanone were obtained as a yellow oil.

5 c) A solution of 2.16 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-isopropyl-1-indanone and 80 mg of p-toluenesulphonic acid in 60 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling
10 solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.4 g (55%) of (RS)-1-(7-isopropyl-1,4-
15 dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 0.84 ml (10.8 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of
20 1.38 g (5.4 mmol) of (RS)-1-(7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.01 ml (21.6 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloro-
25 methane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and
30 evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.7 g (10.8 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of
35 ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The

brown oil obtained was purified by column chromatography on silica gel (toluene). 1.08 g (72%) of (RS)-1-(2-azido-propyl)-7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellow oil.

- 5 e) 1.06 g (3.78 mmol) of (RS)-1-(2-azido-propyl)-7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 110 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed
10 with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 219 mg (1.89 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 15 hours and
15 the white crystals were subsequently filtered off. 918 mg (78%) of (RS)-2-(7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 203° were obtained.

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Example 40

- a) A solution of 2.16 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-isopropyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A
25 solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by
30 column chromatography on silica gel (ethyl acetate/toluene 1:1). 1.78 g (70%) of (R)-1-(7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.
- b) 1.08 ml (13.9 mmol) of methanesulphonyl chloride were
35 added dropwise while stirring to a solution, cooled to 0°, of 1.78 g (6.97 mmol) of (R)-1-(7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.86 ml (27.9 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was

stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 70 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.91 g (13.9 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 150 ml of water and extracted twice with 200 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.12 g (57%) of (S)-1-(2-azido-propyl)-7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

c) 1.12 g (3.99 mmol) of (S)-1-(2-azido-propyl)-7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol were hydrogenated on 112 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 232 mg (2.0 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 5 hours and the white crystals were subsequently filtered off. 371 mg (29%) of (S)-2-(7-isopropyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.57) with m.p. 179-181° were obtained.

Example 41

a) A solution of 11.0 g (58.0 mmol) of 6-tert-butyl-1-indanone, 12.5 ml (145 mmol) of 3-buten-2-ol and 110 mg of p-toluenesulphonic acid in 110 ml of 2,2-dimethoxy-propane was
5 boiled under reflux for 41 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether
10 6:1). 7.35 g (53%) of (RS)-2-(2-buten-1-yl)-6-tert-butyl-1-indanone was obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 35 minutes while stirring through a solution, cooled to -70°, of
15 7.35 g (30.5 mmol) of (RS)-2-(2-buten-1-yl)-6-tert-butyl-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 3.36 ml (45.8 mmol) of dimethyl sulphide the
20 mixture was stirred at room temperature for 17 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 100 ml of dichloromethane and, after the addition of 15 ml of water and 15 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently
25 poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over
30 magnesium sulphate and concentrated in a vacuum. 6.44 g (92%) of (RS)-2-(2-oxoethyl)-6-tert-butyl-1-indanone were obtained as a yellow oil.

c) A solution of 2.3 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-tert-butyl-1-indanone and 80 mg of p-toluenesulphonic acid in
35 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution

over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate /toluene 1:1).

5 1.9 g (70%) of (R)-1-(7-tert-butyl-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.1 ml (14.1 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.9 g
10 (7.05 mmol) of (R)-1-(7-tert-butyl-1,4-dihydro-indeno[1,2-b]-pyrrol-1-yl)-propan-2-ol and 3.9 ml (28.2 mmol) of triethylamine in 55 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloromethane,
15 washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and
20 evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.83 g (12.6 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 120 ml of water and extracted twice with 120 ml of
25 ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on
30 silica gel (toluene). 0.82 g (44%) of (S)-1-(2-azido-propyl)-7-tert-butyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light brown oil.

e) 0.82 g (2.8 mmol) of (S)-1-(2-azido-propyl)-7-tert-butyl-
35 1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol was hydrogenated on 80 mg of platinum oxide for 2 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil

obtained was dissolved in 50 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 163 mg (1.4 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 15 hours and the pale pink
5 coloured crystals were subsequently filtered off. 0.33 g (36%) of (S)-2-(7-tert-butyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 188-190° were obtained.

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Example 42

a) A solution of 9.73 g (45 mmol) of 5'-methoxy-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one, 9.3 ml (108 mol) of 3-buten-2-ol and 100 mg of p-toluenesulphonic
15 acid in 100 ml of 2,2-dimethoxy-propane was boiled under reflux for 90 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 7:1). In
20 addition to 4.0 g of educt there were obtained 6.24 g (51%) of (RS)-2'-(2-buten-1-yl)-5'-methoxy-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one as a yellow oil.

b) An ozone stream (2.5 g ozone/hour) was conducted for 50
25 minutes while stirring through a solution, cooled to -70°, of 6.2 g (22.9 mmol) of (RS)-2'-(2-buten-1-yl)-5'-methoxy-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one in 80 ml of anhydrous dichloromethane and 20 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes
30 and with argon for 10 minutes. After the addition of 2.52 ml (34.4 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 17 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 100 ml of dichloromethane and, after the addition of 15 ml of water and
35 15 ml of trifluoroacetic acid, stirred at room temperature for 2.5 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water

were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 5.74 g (97%) of (RS)-2'-(2-oxoethyl)-5'-methoxy-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one were obtained as a light yellow oil.

c) A solution of 2.58 g (10 mmol) of (RS)-2'-(2-oxoethyl)-5'-methoxy-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 1:1). 1.98 g (67%) of (R)-1-[7'-methoxy-1',4'-dihydro-spiro[cyclopentane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol were obtained as a yellow oil.

d) 1.02 ml (13.1 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.95 g (6.6 mmol) of (R)-1-[7'-methoxy-1',4'-dihydro-spiro[cyclopentane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol and 3.65 ml (26.2 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.86 g (13.2 mmol) of sodium azide and the reaction mixture was heated to 70° for 5 hours while stirring. After cooling the solution was poured into 70 ml of water and

extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 80 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 1.45 g (68%) of (S)-1'-(2-azido-propyl)-7'-methoxy-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrole were obtained as a light yellow oil.

10 e) 1.45 g (4.5 mmol) of (S)-1'-(2-azido-propyl)-7'-methoxy-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrole dissolved in 60 ml of anhydrous ethanol were hydrogenated on 145 mg of platinum oxide for 14 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 522 mg (4.5 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 5 hours and the white crystals were subsequently filtered off. 1.47 g (79%) of (S)-1-methyl-2-(7'-methoxy-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:1) with m.p. 183-185° were obtained.

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Example 43

a) A solution of 2.50 g (116 mmol) of 5'-methyl-2',3'-dihydro-spiro[cyclohexane-1,1'-[1H]indene]-3'-one, 24.1 ml (280 mmol) of 3-buten-2-ol and 250 mg of p-toluenesulphonic acid in 250 ml of 2,2-dimethoxypropane was boiled under reflux for 88 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 6:1). In addition to 8.4 g of educt there were obtained 18.4 g (59%) of (RS)-2'-(3-buten-1-yl)-5'-methyl-2',3'-dihydro-spiro[cyclohexane-1,1'-[1H]indene]-3'-one as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 75 minutes while stirring through a solution, cooled to -70° , of 18.4 g (68.5 mmol) of (RS)-2'-(2-buten-1-yl)-5'-methyl-2',3'-dihydro-spiro[cyclohexane-1,1'-[1H]indene]-3'-one in 300 ml of anhydrous dichloromethane and 60 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 7.55 ml (103 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 200 ml of dichloromethane and, after the addition of 30 ml of water and 30 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 17.0 g (97%) of (RS)-2'-(2-oxoethyl)-5'-methyl-2',3'-dihydro-spiro[cyclohexane-1,1'-[1H]indene]-3'-one were obtained as a yellow oil.

c) A solution of 2.56 g (10 mmol) of (RS)-2'-(2-oxoethyl)-5'-methyl-2',3'-dihydro-spiro[cyclohexane-1,1'-[1H]indene]-3'-one and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane 2:3). 2.45 g (83%) of (R)-1-[7'-methyl-1',4'-dihydro-spiro[cyclohexane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol were obtained as a brown oil.

d) 1.3 ml (16.6 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.45 g (8.3 mmol) of (R)-1-[7'-methyl-1',4'-dihydro-spiro[cyclohexane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol and 4.75 ml (33.2 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 2.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The yellow oil obtained was dissolved in 75 ml of anhydrous dimethylformamide, treated with 1.08 g (16.6 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 90 ml of water and once with 90 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 1.76 g (66%) of (S)-1'-(2-azido-propyl)-7'-methyl-1',4'-dihydro-spiro[cyclohexane]-1,4'-indeno[1,2-b]pyrrole were obtained as a light red oil.

e) 1.76 g (5.49 mmol) of (S)-1'-(2-azido-propyl)-7'-methyl-1',4'-dihydro-spiro[cyclohexane]-1,4'-indeno[1,2-b]pyrrole dissolved in 100 ml of anhydrous ethanol was hydrogenated on 170 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The light brown oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 637 mg (5.49 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 22 hours and the white crystals were subsequently filtered off. 1.7 g (76%) of (S)-1-methyl-2-(7'-

methyl-1',4'-dihydro-spiro[cyclohexane]-1,4'-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:1) with m.p. 195-196° were obtained.

Example 44

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a) A solution of 17.0 g (84.8 mmol) of 5'-methyl-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one, 17.5 ml (204 mol) of 3-buten-2-ol and 170 mg of p-toluenesulphonic acid in 170 ml of 2,2-dimethoxy-propane was boiled under reflux for 71 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). In addition to 15 4.0 g of educt there were obtained 12.7 g (59%) of (RS)-2'-(2-buten-1-yl)-5'-methyl-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 60 minutes while stirring through a solution, cooled to -70°, of 20 12.7 g (50.1 mmol) of (RS)-2'-(2-buten-1-yl)-5'-methyl-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one in 250 ml of anhydrous dichloromethane and 50 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 5.54 ml 25 (75.5 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 17 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 160 ml of dichloromethane and, after the addition of 15 ml of water and 30 15 ml of trifluoroacetic acid, stirred at room temperature for 2.5 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was 35 extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 12.0 g (99%) of (RS)-2'-(2-oxoethyl)-

5'-methyl-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one were obtained as a light red oil.

- c) A solution of 2.42 g (10 mmol) of (RS)-2'-(2-oxoethyl)-5'-methyl-2',3'-dihydro-spiro[cyclopentane-1,1'-[1H]indene]-3'-one and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 3:2). 2.06 g (73%) of (R)-1-[7'-methyl-1',4'-dihydro-spiro[cyclopentane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol were obtained as a red oil.
- d) 1.15 ml (14.6 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.06 g (7.32 mmol) of (R)-1-[7'-methyl-1',4'-dihydro-spiro[cyclopentane-1,4'-indeno[1,2-b]pyrrole]-1'-yl]-propan-2-ol and 4.03 ml (14.6 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 75 ml of anhydrous dimethylformamide, treated with 0.95 g (14.6 mmol) of sodium azide and the reaction mixture was heated to 70° for 5 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated

in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). 1.34 g (66%) of (S)-1'-(2-azido-propyl)-7'-methyl-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrole were obtained as a light red oil.

e) 1.34 g (4.37 mmol) of (S)-1'-(2-azido-propyl)-7'-methyl-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrole dissolved in 75 ml of anhydrous ethanol was hydrogenated on 135 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 507 mg (4.37 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 15 hours and the white crystals were subsequently filtered off. 1.23 g (71%) of (S)-1-methyl-2-(7'-methyl-1',4'-dihydro-spiro[cyclopentane]-1,4'-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:1) with m.p. 192° were obtained.

20

Example 45

a) A solution of 1.05 g (4.13 mmol) of (RS)-1-(2-azido-propyl)-7-hydroxy-1,4-dihydro-indeno[1,2-b]pyrrole, 0.77 ml (8.26 mmol) of isopropyl bromide and 1.14 g (8.26 mmol) of potassium carbonate in 30 ml of N,N-dimethylformamide was heated to 50° for 48 hours. After cooling the solution was poured into 150 ml of water and extracted twice with 150 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of semi-saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The crude product was purified by column chromatography on silica gel (toluene). 0.35 g (28%) of (RS)-1-(2-azido-propyl)-7-iso-propoxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as an orange oil which was used directly in the next reaction.

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b) 0.35 g (1.17 mmol) of (RS)-1-(2-azido-propyl)-7-isopropoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 40 ml of anhydrous ethanol was hydrogenated on 40 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed
5 with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 68 mg (0.58 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the
10 white crystals were subsequently filtered off. 0.22 mg (57%) of (RS)-2-(7-isopropoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 192° was obtained.

Example 46

15

a) A solution of 8.0 g (54 mmol) of 6-hydroxy-1-indanone, 6.3 ml (59.4 mmol) of cyclopentyl bromide, 16.4 g (119 mmol) of potassium carbonate and 10 ml of N,N-dimethylformamide in 100 ml of acetone was heated to 75° for 35 hours. After cooling
20 the solution was poured into 150 ml of water and extracted twice with 200 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a
25 vacuum. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 3:1). 9.45 g (81%) of 6-cyclopentoxy-1-indanone were obtained as an orange oil which was used directly in the next reaction.

30 b). A solution of 9.45 g (43.7 mmol) of 6-cyclopentoxy-1-indanone, 9.0 ml (105 mmol) of 3-buten-2-ol and 100 mg of p-toluenesulphonic acid in 100 ml of 2,2-dimethoxy-propane was boiled under reflux for 63 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction
35 mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 6:1). There were obtained 8.1 g (69%) of (RS)-2-(2-buten-1-yl)-6-cyclopentoxy-1-indanone as a yellow oil.

c) An ozone stream (1.5 g ozone/hour) was conducted for 60 minutes while stirring through a solution, cooled to -70° , of 8.1 g (29.9 mmol) of (RS)-2-(2-buten-1-yl)-6-cyclopentoxo-1-indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 3.29 ml (44.9 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 21 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 75 ml of dichloromethane and, after the addition of 12.5 ml of water and 12.5 ml of trifluoroacetic acid, stirred at room temperature for 5 hours. The mixture was subsequently poured into 150 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 5.63 g (73%) of (RS)-2-(2-oxoethyl)-6-cyclopentoxo-1-indanone were obtained as an orange oil.

d) A solution of 2.58 g (10 mmol) of (RS)-2-(2-oxoethyl)-6-cyclopentoxo-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.44 g (48%) of (RS)-1-(7-cyclopentoxo-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a light yellow oil.

35

d) 0.75 ml (9.6 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0° , of 1.44 g (4.8 mmol) of (RS)-1-(7-cyclopentoxo-1,4-dihydro-

- indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.66 ml (19.3 mmol) of triethylamine in 55 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of
- 5 dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and
- 10 evaporated in a vacuum. The green oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 0.62 g (9.6 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 100 ml of water and extracted twice with 100 ml of
- 15 ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on
- 20 silica gel (ethyl acetate/hexane 1:4). 1.27 g (82%) of (RS)-1-(2-azido-propyl)-7-cyclopentoxo-1,4-dihydro-indeno[1,2-b]pyrrole were obtained as a light yellowish solid which was used directly in the next reaction.
- 25 f) 1.27 g (3.93 mmol) of (RS)-1-(2-azido-propyl)-7-cyclopentoxo-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 75 ml of anhydrous ethanol was hydrogenated on 125 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The
- 30 light red oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 198 mg (1.7 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 17 hours and the pale pink coloured crystals were subsequently filtered off.
- 35 926 mg (80%) of (RS)-2-(7-cyclopentoxo-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:0.5) with m.p. 196-198° were obtained.

Example 47

a) 12.6 ml (162 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of
5 12.0 g (81 mmol) of 6-hydroxy-1-indanone and 45.2 ml (162 mmol) of triethylamine in 350 ml of dichloromethane and the solution was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of dichloromethane, washed twice with 150 ml of
10 saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 100 ml of dichloromethane. The combined organic phases were washed with 200 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. 18.3 g (99%) of
15 6-mesyloxy-1-indanone were obtained as a brown solid which was used directly in the next reaction.

b) A solution of 18.3 g (80.9 mmol) of 6-mesyloxy-1-indanone, 16.7 ml (194 mmol) of 3-buten-2-ol and 300 mg of p-toluenesulphonic acid in 400 ml of 2,2-dimethoxy-propane was
20 boiled under reflux for 46 hours on a water-separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate
25 4:1). In addition to 8.31 g of educt there were obtained 11.3 g (50%) of (RS)-2-(2-buten-1-yl)-6-mesyloxy-1-indanone as a yellow oil.

c) An ozone stream (2 g ozone/hour) was conducted for 55
30 minutes while stirring through a solution, cooled to -70°, of 11.3 g (40.3 mmol) of (RS)-2-(2-buten-1-yl)-6-mesyloxy-1-indanone in 300 ml of anhydrous dichloromethane and 60 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the
35 addition of 4.51 ml (61.5 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 250 ml of dichloromethane and, after the addition of

25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 4 hours. The mixture was subsequently poured into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further
5 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 9.38 g (85%) of (RS)-2-(2-oxoethyl)-6-mesyloxy-1-indanone were obtained as
10 a light brown solid with m.p. 85-87°.

d) A solution of 2.31 g (8.59 mmol) of (RS)-2-(2-oxoethyl)-6-mesyloxy-1-indanone and 110 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A
15 solution of 2.58 g (34.4 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture
20 was purified by column chromatography on silica gel (ethyl acetate/hexane 2:3). 0.74 g (28%) of (RS)-1-(7-mesyloxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol was obtained as a light brown solid which was used directly in the next reaction.

25 e) 0.37 ml (4.77 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.72 g (2.38 mmol) of (RS)-1-(7-mesyloxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 1.33 ml (9.53 mmol) of triethylamine in 30 ml of dichloromethane and the mixture was
30 stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The
35 combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green oil obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 0.62 g

(4.77 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were
5 washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (ethyl acetate/hexane 1:4). 0.68 g (86%) of (RS)-1-(2-
10 azido-propyl)-7-mesyloxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellowish solid which was used directly in the next reaction.

f) 0.66 g (2.0 mmol) of (S)-1-(2-azido-propyl)-7-mesyloxy-
15 1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol was hydrogenated on 66 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The light brown oil
obtained was dissolved in 50 ml of anhydrous diethyl ether,
20 filtered and treated while stirring with a solution of 116 mg (1.0 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 17 hours and the pale pink coloured crystals were subsequently filtered off. 400 mg (55%)
of (RS)-2-(7-mesyloxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-
25 methyl-ethylamine fumarate (1:0.5) with m.p. 201° were obtained.

Example 48

30 a) A lithium diisopropylamide solution, freshly prepared from 4.25 ml (30.0 mmol) of diisopropylamine and 18.7 ml (30 mmol) of 1.6N n-butyllithium in hexane, in 60 ml of anhydrous tetrahydrofuran was added dropwise while stirring to a solution, cooled to -70°, of 3.24 g (20.0 mmol) of 5-methoxy-1-indanone
35 in 350 ml of anhydrous tetrahydrofuran. The mixture was stirred at this temperature for a further 30 minutes and a solution of 1.6 ml (20.0 mmol) of chloroacetone dissolved in 60 ml of anhydrous tetrahydrofuran was subsequently added dropwise over

15 minutes. The reaction mixture was left to come to room temperature over 100 minutes and was stirred at this temperature for a further 45 minutes. Subsequently, the reaction mixture was poured on to 150 ml of ice, 150 ml of saturated sodium chloride were added and the organic phase was separated. The aqueous phase was extracted once with 400 ml of diethyl ether, the combined organic phases were washed once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The red oil obtained was purified by column chromatography on silica gel (hexane/diethyl ether 3:7). There were obtained 1.67 g of crude product which was crystallized from diethyl ether/hexane. The crystallization gave 1.21 g (56%) of (RS)-5-methoxy-2-(2-oxopropyl)-1-indanone as a light yellow solid with m.p. 73°.

b) A solution of 1.2 g (5.5 mmol) of (RS)-5-methoxy-2-(2-oxopropyl)-1-indanone and 60 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 1.65 g (22.0 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 90 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.17 g (82%) of (RS)-1-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as a yellow solid which was used without further crystallization in the next reaction.

c) 0.7 ml (9.0 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.16 g (4.51 mmol) of (RS)-1-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.5 ml (18.0 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 100 ml of dichloromethane, washed twice with 60 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases

were extracted once with 60 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.58 g (9.0 mmol) of sodium azide and the reaction mixture was heated to 80° for 16 hours while stirring. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.86 g (68%) of (RS)-1-(2-azido-propyl)-6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a yellow oil.

d) 0.85 g (3.01 mmol) of (S)-1-(2-azido-propyl)-6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 85 mg of platinum oxide for 17 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The light yellow oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 175 mg (1.51 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 19 hours and the slightly white crystals were subsequently filtered off. 779 mg (82%) of (S)-2-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 218° were obtained.

Example 49

a) A solution of 12.3 g (61.2 mmol) of 5,6-dichloro-1-indanone, 12.6 ml (0.15 mol) of 3-buten-2-ol and 125 mg of p-toluenesulphonic acid in 125 ml of 2,2-dimethoxy-propane was boiled under reflux for 68 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction

mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). In addition to 4.3 g of educt there were obtained 10.8 g (69%) of (RS)-2-(2-buten-1-yl)-5,6-dichloro-1-indanone as a
5 yellow oil.

b) An ozone stream (3.5 g ozone/hour) was conducted for 45 minutes while stirring through a solution, cooled to -70° , of 10.8 g (42.4 mmol) of (RS)-2-(2-buten-1-yl)-5,6-dichloro-1-
10 indanone in 150 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.66 ml (63.6 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 3 hours. The
15 reaction mixture was evaporated in a vacuum, the residue was treated with 150 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise
20 addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There were
25 obtained 11.6 g of crude product which was crystallized from hexane/ethyl acetate. The crystallization gave 7.59 g (73%) of (RS)-2-(2-oxoethyl)-5,6-dichloro-1-indanone as a light yellow solid with m.p. $93-96^{\circ}$.

30 c) A solution of 2.0 g (8.23 mmol) of (RS)-2-(2-oxoethyl)-5,6-dichloro-1-indanone and 70 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.47 g (32.9 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling
35 solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl

ether/hexane 4:1). 0.62 g (27%) of (RS)-1-(6,7-dichloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol was obtained as a brown oil.

5 d) 0.33 ml (4.25 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.6 g (2.12 mmol) of (RS)-1-(6,7-dichloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 1.18 ml (8.5 mmol) of triethyl-
10 amine in 30 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 50 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate
15 solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated
20 in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 275 mg (4.24 mmol) of sodium azide and the reaction mixture was heated to 60° for 17 hours while stirring. After cooling the solution was poured
25 into 60 ml of water and extracted three times with 90 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The
brown oil obtained was purified by column chromatography on silica gel (toluene). 0.45 g (69%) of (RS)-1-(2-azido-propyl)-6,7-dichloro-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a
light colourless oil.

30

e) 0.44 g (1.43 mmol) of (RS)-1-(2-azido-propyl)-6,7-dichloro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol was hydrogenated on 45 mg of platinum oxide
for 3 hours. The catalyst was subsequently filtered off, rinsed
35 with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 30 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 83 mg (0.72 mmol) of fumaric acid in 5 ml of methanol. The

mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 395 mg (81%) of (RS)-2-(6,7-dichloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 203° were
5 obtained.

Example 50

a) A solution of 13.0 g (89 mmol) of 4-methyl-1-indanone,
10 19.2 ml (0.22 mol) of 3-buten-2-ol and 170 mg of p-toluene-sulphonic acid in 170 ml of 2,2-dimethoxy-propane was boiled under reflux for 46 hours on a water separator filled with molecular sieve (0.4 nm, 2 mm pearl shaped). The reaction mixture was subsequently concentrated in a vacuum and purified
15 by column chromatography on silica gel (hexane/diethyl ether 5:1). 12.0 g (67%) of (RS)-2-(2-buten-1-yl)-4-methyl-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted for 90
20 minutes while stirring through a solution, cooled to -70°, of 12.0 g (60 mmol) of (RS)-2-(2-buten-1-yl)-4-methyl-1-indanone in 220 ml of anhydrous dichloromethane and 45 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the
25 addition of 6.6 ml (90 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 160 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room
30 temperature for 2 hours. The mixture was subsequently poured into 200 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 200 ml of dichloro-
35 methane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 10.6 g (94%) of (RS)-2-(2-oxoethyl)-4-methyl-1-indanone were obtained as a light yellow oil.

- c) A solution of 1.9 g (10.0 mmol) of (RS)-2-(2-oxoethyl)-4-methyl-1-indanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 45 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 0.63 g (28%) of (RS)-1-(5-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol was obtained as a white solid which was used directly in the next reaction.
- d) 0.44 ml (5.6 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.63 g (2.8 mmol) of (RS)-1-(5-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 1.6 ml (11.2 mmol) of triethylamine in 25 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 50 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The green solid obtained was dissolved in 30 ml of anhydrous dimethylformamide, treated with 0.36 g (5.6 mmol) of sodium azide and the reaction mixture was heated to 60° for 16 hours while stirring. After cooling the solution was poured into 80 ml of water and extracted three times with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.69 g (98%) of (RS)-1-(2-azido-propyl)-5-methyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a light yellow oil.

e) 0.69 g (2.7 mmol) of (RS)-1-(2-azido-propyl)-5-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol was hydrogenated on 70 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 80 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 157 mg (1.35 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 0.34 g (44%) of (RS)-2-(5-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 214° were obtained.

15

Example 51

a) An ozone stream (3 g ozone/hour) was conducted while stirring during 55 minutes through a solution, cooled to -70°, of 10.1 g (50 mmol) of (RS)-2-(2-buten-1-yl)-4-chromanone) in 100 ml of anhydrous dichloromethane and 300 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 15 minutes. After the addition of 5 ml (67.7 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was dissolved with 5.62 g (55 mmol) of N-acetyleneethylenediamine in 100 ml of concentrated acetic acid and boiled under reflux for 45 minutes. The reaction mixture was subsequently concentrated in a vacuum and the residue was purified by column chromatography on silica gel (ethyl acetate). There were obtained 5.7 g (45%) of N-[2-(1,4-dihydro[1]benzopyrano[4,3-b]pyrrol-1-yl)-ethyl]-acetamide as a brown solid which was used in the next reaction without further recrystallization.

b) A mixture of 2.5 g (9.7 mmol) of N-[2-(1,4-dihydro[1]benzopyrano[4,3-b]pyrrol-1-yl)-ethyl]-acetamide, 3.28 g (58 mmol) of potassium hydroxide, 20 ml of water and 40 ml of ethylene glycol was heated to 110° while stirring for 23 hours.

After cooling the reaction mixture was poured into 100 ml of saturated sodium chloride solution and extracted three times with 200 ml of ethyl acetate each time. The organic phases were washed once with 200 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The residue was purified by column chromatography on silica gel (dichloromethane/methanol/ammonia 200:10:1). The oil obtained was dissolved in 110 ml of anhydrous diethyl ether, filtered and treated with a solution of 436 mg (3.8 mmol) of fumaric acid in 20 ml of anhydrous methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off under suction. 812 mg (31%) of 2-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-ethylamine fumarate (1:0.5) with m.p. 180° were obtained.

Example 52

a) A solution of 1.9 g (10 mmol) of (RS)-2-(2-oxoethyl)-4-chromanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (R)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.9 g (83%) of (R)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol were obtained as a yellow oil.

b) 1.27 ml (16.4 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.88 g (8.2 mmol) of (R)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol and 4.57 ml (32.8 mmol) of triethylamine in 50 ml of anhydrous dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 280 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous

phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown solid obtained was dissolved
5 in 50 ml of anhydrous dimethylformamide, treated with 1.0 g (15.2 mmol) of sodium azide and the reaction mixture was heated to 60° for 18 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were
10 washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.67 g (80%) of (S)-1-(2-azido-propyl)-1,4-
15 dihydro-[1]benzopyrano[4,3-b]-pyrrole were obtained as a colourless oil.

c) 1.65 g (6.5 mmol) of (S)-1-(2-azido-propyl)-1,4-dihydro-[1]benzopyrano[4,3-b]-pyrrole dissolved in 60 ml of anhydrous
20 ethanol were hydrogenated on 170 mg of platinum oxide for 4 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The thus-obtained colourless oil was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution
25 of 309 mg (2.67 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 1.35 g (73%) of (S)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 194-195° were
30 obtained.

Example 53

a) A solution of 25 g (0.15 mol) of 5-chloro-1-indanone,
35 31 ml (0.36 mol) of 3-buten-2-ol and 250 mg of p-toluene-sulphonic acid in 31 ml of 2,2-dimethoxypropane and 250 ml of anhydrous toluene was boiled under reflux for 17 hours. The reaction mixture was subsequently concentrated in a vacuum and

purified by column chromatography on silica gel (hexane/diethyl ether 5:1). 11.9 g (36%) of (RS)-2-(2-buten-1-yl)-5-chloro-1-indanone were obtained as a yellow oil.

5 b) An ozone stream (3 g ozone/hour) was conducted while stirring during 60 minutes through a solution, cooled to -70° , of 11.9 g (53.9 mmol) of (RS)-2-(2-buten-1-yl)-5-chloro-1-indanone in 200 ml of anhydrous dichloromethane and 100 ml of anhydrous methanol. Subsequently, the solution was flushed with
10 oxygen for 5 minutes and with argon for 10 minutes. After the addition of 5.9 ml (80.9 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 50 ml of dichloromethane and, after the addition of 12 ml
15 of water and 12 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of water were added, the phases were separated and the
20 aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was crystallized from ethyl acetate/hexane. 8.98 g (80%) of (RS)-2-(2-oxoethyl)-6-chlor-1-indanone were
25 obtained as a white solid with m.p. 66° .

c) A solution of 2 g (9.6 mmol) of (RS)-2-(2-oxoethyl)-6-chlor-1-indanone and 100 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A
30 solution of 2.88 g (38.3 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 30 ml. The cooled reaction mixture
35 was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). There were obtained 1.9 g (80%) of (RS)-1-(6-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol as a brown oil which was used directly in the next reaction.

d) 1.2 ml (15.3 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.9 g (7.7 mmol) of (RS)-1-(6-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 4.3 ml (30.6 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of dichloromethane, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of dichloromethane. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 1.0 g (15.3 mmol) of sodium azide and the reaction mixture was heated to 50° for 17 hours while stirring. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time and once with 140 ml of ethyl acetate. The combined organic phases were washed once with 140 ml of water and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.8 g (38%) of (RS)-1-(2-azido-propyl)-6-chloro-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a yellowish oil.

e) 0.8 g (2.9 mmol) of (RS)-1-(2-azido-propyl)-6-chloro-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 80 ml of anhydrous ethanol were hydrogenated on 80 mg of platinum oxide for 3 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 150 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 170 mg (1.46 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 4 hours and the white crystals were subsequently filtered off. 780 mg (87%) of

(RS)-2-(6-chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 212° were obtained.

Example 54

5

a) A solution 11.9 g (66.7 mmol) of 7-methoxy-4-chromanone, 13.8 ml (0.16 mol) of 3-buten-2-ol and 120 mg of p-toluenesulphonic acid in 14 ml of 2,2-dimethoxypropane and 120 ml of anhydrous toluene was boiled under reflux for 24
10 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 6.3 g (41%) of (RS)-2-(2-buten-1-yl)-7-methoxy-4-chromanone were obtained as a yellow oil.

15

b) An ozone stream (3 g ozone/hour) was conducted while stirring for 1 hour through a solution, cooled to -70°, of 6.25 g (26.9 mmol) of (RS)-2-(2-buten-1-yl)-7-methoxy-4-chromanone in 90 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for
20 5 minutes and with argon for 15 minutes. After the addition of 3 ml (40.5 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was subsequently evaporated in a vacuum, the residue was treated with 60 ml of dichloromethane and, after the addition of 15 ml
25 of water and 15 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 100 ml of water and neutralized while stirring by the spatula-wise addition of sodium hydrogen carbonate. A further 70 ml of water were added, the phases were separated and the
30 aqueous phase was extracted twice with 100 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. 2.9 g (49%) of 2-(2-oxoethyl)-7-methoxy-4-chromanone were obtained as a yellow oil.

35

c) A solution of 2.38 g (10.8 mmol) of (RS)-2-(2-oxoethyl)-7-methoxy-4-chromanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator.

A solution of 3.25 g (43.2 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.95 g (70%) of (RS)-1-(1,4-dihydro-8-methoxy[1]-benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol were obtained as a brown oil.

d) 1.15 ml (14.8 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.92 g (7.4 mmol) of (RS)-1-(1,4-dihydro-8-methoxy[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol and 4.13 ml (29.6 mmol) of triethylamine in 50 ml of anhydrous dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 280 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.96 g (14.8 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 18 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.58 g (75%) of (RS)-1-(2-azido-propyl)-1,4-dihydro-8-methoxy-[1]benzopyrano[4,3-b]pyrrole were obtained as a colourless oil.

e) 1.57 g (5.5 mmol) of (RS)-1-(2-azido-propyl)-1,4-dihydro-8-methoxy-[1]benzopyrano[4,3-b]pyrrole dissolved in 60 ml of

anhydrous ethanol were hydrogenated on 160 mg of platinum oxide for 17 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 281 mg (2.45 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 1.42 g (86%) of (RS)-1-(1,4-dihydro-[1]benzopyrano-[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 197-198° were obtained.

Example 55

a) A solution of 50.0 g (0.31 mol) of 5-methoxy-1-indanone, 80 ml (0.92 mol) of 3-buten-2-ol, 132 ml (1.08 mol) of 2,2-dimethoxypropane and 600 mg of p-toluenesulphonic acid in 500 ml of toluene was brought to boiling. The resulting methanol/acetone mixture was distilled off and the reaction solution was subsequently boiled under reflux for a further 48 hours. After cooling the solution was evaporated in a vacuum. Purification on silica gel (hexane/diethyl ether 5:1) yielded 19.2 g (31%) of (RS)-2-(2-buten-1-yl)-5-methoxy-1-indanone as a pale yellow oil.

b) Ozone (3 g ozone/hour) was conducted while stirring for 85 minutes through a solution, cooled to -70°, of 19.2 g (89 mmol) of (RS)-2-(2-buten-1-yl)-5-methoxy-1-indanone in 600 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen and then 9.1 ml (0.12 mol) of dimethyl sulphide were added to the cold solution. The solution came to room temperature overnight and was evaporated in a vacuum. The residue was chromatographed (dichloromethane) over a column with oxalic acid solution adsorbed on silica gel (600 g silica gel; 100 ml 10% oxalic acid solution). 14.1 g (78%) of (RS)-2-(2-oxoethyl)-5-methoxy-1-indanone were obtained as a yellow oil.

c) An ozone stream (3 g ozone/hour) was conducted while stirring during 60 minutes through a solution, cooled to -70° , of 13.3 g (61.5 mmol) of (RS)-2-(2-oxoethyl)-5-methoxy-1-indanone in 200 ml of anhydrous dichloromethane and 100 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 6.82 ml (92.2 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 200 ml of dichloromethane and, after the addition of 25 ml of water and 25 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 100 ml of water and neutralized while stirring by the spatula-wise addition of sodium hydrogen carbonate. A further 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There were obtained 11.6 g (92%) of (RS)-2-(2-oxoethyl)-5-methoxy-1-indanone as a yellow oil which was used in the next reaction without further purification.

d) A solution of 2 g (9.8 mmol) of (RS)-2-(2-oxoethyl)-5-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 2.94 g (39.2 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). There were obtained 1.6 g (67%) of (RS)-1-(6-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol as a brown oil which was used directly in the next reaction.

e) 1.9 ml (11.6 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0° , of 1.41 g (5.8 mmol) of (RS)-1-(6-methoxy-1,4-dihydro-indeno-

[1,2-b]pyrrol-1-yl)-propan-2-ol and 3.24 ml (23.2 mmol) of triethylamine in 50 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 150 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 558 mg (8.6 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 7 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 140 ml of water and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.75 g (48%) of (RS)-1-(2-azido-propyl)-6-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

f) 0.75 g (2.8 mmol) of (RS)-1-(2-azido-propyl)-6-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 30 ml of anhydrous ethanol was hydrogenated on 60 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 50 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 324 mg (2.79 mmol) of fumaric acid in 50 ml of methanol. The mixture was stirred at room temperature for 16 hours and the white crystals were subsequently filtered off. 530 mg (63%) of (RS)-2-(6-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 189° were obtained.

Example 55

a) A solution of 1.9 g (10 mmol) of (RS)-2-(2-oxoethyl)-4-chromanone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (S)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). 1.73 g (76%) of (S)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol were obtained as a yellow oil.

b) 1.15 ml (14.8 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.7 g (7.4 mmol) of (S)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol and 4.13 ml (29.7 mmol) of triethylamine in 50 ml of anhydrous dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown solid obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.88 g (13.5 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 18 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.49 g (79%) of (R)-1-(2-azido-propyl)-1,4-dihydro-[1]benzopyrano[4,3-b]pyrrole were obtained as a colourless oil.

- c) 1.47 g (5.8 mmol) of (R)-1-(2-azido-propyl)-1,4-dihydro-[1]benzopyrano[4,3-b]-pyrrole dissolved in 60 ml of anhydrous ethanol were hydrogenated on 150 mg of platinum oxide for 18 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 294 mg (2.53 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 18 hours and the white crystals were subsequently filtered off. 1.3 g (79%) of (R)-1-(1,4-dihydro-[1]benzopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) m.p. 194-195° were obtained.

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Example 57

- a) 0.5 g (1.8 mmol) of N-[2-(4,5-dihydro-7-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 23 hours under argon in 21 ml of ethylene glycol/water 2:1 in the presence of 0.60 g (10.7 mmol) of potassium hydroxide. The reaction mixture was left to cool and poured into 100 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether, the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 20 ml of diethyl ether and added dropwise to a solution of 245 mg (2.11 mmol) of fumaric acid in 20 ml of methanol. The mixture was left to stir for one hr. and the yellowish crystals were filtered off under suction. 241 mg (38%) of 2-(4,5-dihydro-7-methoxy-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:0.8) with m.p. 195° were obtained.

Example 58

- a) 35.25 g (0.2 mol) of 5-methoxy-1-tetralone and 61 ml (0.8 mol) of N,N-dimethylhydrazine were heated to about 80° under argon for 5 hours. The mixture was left to cool, 200 ml of 10% sodium chloride solution were added and the mixture was

extracted several times with diethyl ether. The mixture was dried over sodium sulphate, filtered and evaporated. The oily residue was distilled over a 10 cm Vigreux column. At 85-95°/0.1 mbar there were obtained 36.4 g (83%) of 5-methoxy-1-tetralone N,N-dimethylhydrazone as a yellow oil.

b) 3.12 g (14.3 mmol) of 5-methoxy-1-tetralone N,N-dimethylhydrazone and 4.15 ml of DMPU were dissolved in 70 ml of absolute THF under argon and cooled to -75°. 10.7 ml of a 1.6M solution of n-butyllithium in hexane were added dropwise. The mixture was stirred at -75° for 1 hour and thereupon treated slowly with 2.0 ml (17.1 mmol) of bromoacetaldehyde dimethyl acetal. The mixture was left to warm to room temperature and stirred for 26 hours. 20 ml of water were added at about 0° and the mixture was extracted three times with ethyl acetate. After drying over sodium sulphate the mixture was filtered, evaporated and the residue was chromatographed on silica gel with toluene, then with toluene/ethyl acetate 9:1. 1.62 g (37%) of 2-(2,2-dimethoxy-1-ethyl)-5-methoxy-1-tetralone N,N-dimethylhydrazone were obtained as an oil.

c) 280 mg (0.9 mmol) of 2-(2,2-dimethoxy-1-ethyl)-5-methoxy-1-tetralone N,N-dimethylhydrazone were dissolved in 12.5 ml of THF and added to 5 ml of phosphate buffer (prepared from 2 ml of 1/15M potassium dihydrogen phosphate and 3 ml of 1/15M disodium hydrogen phosphate) as well as 156 mg of copper (II) chloride dihydrate. After stirring at room temperature for 3.5 hours the reaction had finished. The mixture was treated with 10 ml of 20% ammonium chloride solution and 0.8 ml of conc ammonia. Then, the mixture was extracted several times with ethyl acetate, dried over sodium sulphate, filtered and evaporated. The residue was chromatographed on silica gel firstly with toluene, then with toluene/ethyl acetate 9:1. 180 mg (80%) of 2-(2-oxoethyl)-5-methoxy-1-tetralone were obtained as a yellowish oil (R_f = 0.31, silica gel (toluene/ethyl acetate 9:1)).

d) 175 mg (0.7 mmol) of 2-(2-oxoethyl)-5-methoxy-1-tetralone and 144 mg (1.4 mmol) of N-acetylenediamine

were heated to reflux under argon in 4 ml of acetic acid for 1.5 hours. The solvent was removed in a vacuum, the residue was taken up in 25 ml of water and extracted several times with dichloromethane. Chromatography on 20 g of silica gel with ethyl acetate gave a greenish coloured oil. This was crystallized from toluene for purification. 91 mg (46%) of N-[2-(4,5-dihydro-6-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide with m.p. 133° were obtained.

- 10 e) 3.34 g (11.7 mmol) of N-[2-(4,5-dihydro-6-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 23 hr. under argon in 75 ml of ethylene glycol/water 2:1 in the presence of 3.93 g (58.8 mmol) of potassium hydroxide. The reaction mixture was left to cool and was poured into 300 ml of
15 semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 30 ml of methanol and treated with 1.61 g (13.8 mmol) of fumaric acid. The separated crystals were recrystallized from
20 a total of 140 ml of methanol. 3.8 g (90%) of 2-(4,5-dihydro-6-methoxy-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) were obtained as yellowish crystals with m.p. 198°.

Example 59

- 25 a) 6.30 g (22.2 mmol) of N-[2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 21 hours under argon in 64 ml of ethylene glycol/water 2:1 in the presence of 7.40 g (132 mmol) of potassium hydroxide. The
30 reaction mixture was left to cool and was poured into 250 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether, the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product
35 was dissolved in 100 ml of methanol and treated with 2.6 g (22.4 mmol) of fumaric acid. The separated crystals were recrystallized from a total of 340 ml of methanol. 3.8 g (49%) of 2-(4,5-dihydro-8-methoxy-1H-benz[g]indol-1-yl)-ethylamine

fumarate (1:1) were obtained as yellowish crystals with m.p. 183-185°.

Example 60

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a) 8.85 g (49.0 mmol) of 8-chloro-1-tetralone were dissolved in 90 ml of tetrachloromethane under argon and added to 21.0 ml (245 mmol) of 3-buten-2-ol and 190 mg of p-toluenesulphonic acid. The reaction solution was heated to reflux on a water
10 separator for 9 days. The solvent was removed in a vacuum and the residue was chromatographed on 200 g of silica gel firstly with hexane/ethyl acetate 9:1 and then with hexane/ethyl acetate 4:1. In addition to large amounts of unreacted educt (8.3 g) there were obtained 4.1 g (35%) of 2-(2-buten-1-yl)-8-chloro-1-
15 tetralone as a yellow oil.

b) 7.7 g (32.8 mmol) of 2-(2-buten-1-yl)-8-chloro-1-tetralone were dissolved in a mixture of 220 ml of dichloromethane and 60 ml of methanol, cooled to -75° and the double bond was
20 ozonized in the usual manner. After flushing the reaction mixture with oxygen and argon 4.8 ml (65.6 mmol) of dimethyl sulphide were added dropwise. The mixture was left to warm slowly to room temperature and was stirred for a further 15 hours. The crude product (10.8 g) was dissolved in about 100 ml of di-
25 chloromethane and added to a mixture of 12 ml of 10% aqueous oxalic acid, 120 g of silica gel and 300 ml of dichloromethane. The mixture was stirred at room temperature for 2 hours. 6.4 g (83%) of 8-chloro-2-(2-oxoethyl)-1-tetralone were obtained as a pale brown oil by extraction with dichloromethane.

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c) 325 mg (1.46 mmol) of 8-chloro-2-(2-oxoethyl)-1-tetralone and 290 mg (2.84 mmol) of N-acetylenediamine were heated to reflux in 14 ml of acetic acid under argon for 1 hour. The solvent was removed in a vacuum and the residue was taken
35 up in 10 ml of water and extracted several times with ethyl acetate. Chromatography on 20 g of silica gel with hexane/ethyl acetate 1:1 and then with ethyl acetate gave 190 mg (45%) of N-

[2-(9-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)ethyl]-acetamide as yellowish crystals with m.p. 146-147°.

d) 1.55 g (5.3 mmol) of N-[2-(9-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 21 hours under argon in 23 ml of ethylene glycol/water 2:1 in the presence of 1.80 g (32.1 mmol) of potassium hydroxide. The reaction mixture was left to cool and was poured into 60 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether, the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 10 ml of methanol and treated with 0.62 g (5.3 mmol) of fumaric acid. The separated crystals were recrystallized from a total of 20 ml of methanol. 1.26 g (65%) of 2-(9-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)-ethylamine fumarate were obtained as yellowish crystals with m.p. 181-183°.

Example 61

1.80 g (6.2 mmol) of N-[6-chloro-2-(4,5-dihydro-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 20 hours under argon in 17 ml of ethylene glycol/water 12:5 in the presence of 0.9 g (16.1 mmol) of potassium hydroxide. The mixture was left to cool and was treated with 140 ml of semi-saturated sodium chloride solution. The mixture was extracted three times with diethyl ether, the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The brown oil was chromatographed on 50 g of silica gel with dichloromethane/methanol (19:1, then 9:1). The crude product was dissolved in 7 ml of diethyl ether and 0.98 g (8.4 mmol) of fumaric acid was added. The solvent was removed in a vacuum and the residue was recrystallized from 50 ml of chloroform/ethanol 4:1. 1.41 g (62%) of 2-(6-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) with m.p. 187-188° were obtained.

Example 62

0.5 g (1.7 mmol) of N-[7-chloro-2-(4,5-dihydro-1H-benz[g]indol-1-yl)ethyl]-acetamide was heated to 140° for
5 22 hours under argon in 4.5 ml of ethylene glycol/water 2:1 in the presence of 0.25 g (4.5 mmol) of potassium hydroxide. The mixture was left to cool and was treated with 40 ml of water and 10 ml of saturated sodium chloride solution. The mixture was extracted three times with diethyl ether, the combined
10 extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 30 ml of diethyl ether and added dropwise to a suspension of 208 mg (1.79 mmol) of fumaric acid in 30 ml of diethyl ether. The solvent was removed in a vacuum
15 and the residue was recrystallized from 75 ml of ethanol/ethyl acetate 3:2. 355 mg (58%) of 2-(7-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) with m.p. 176-177° were obtained as white crystals.

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Example 63

1.0 g (3.4 mmol) g of N-[8-chloro-2-(4,5-dihydro-1H-benz[g]indol-1-yl)ethyl]-acetamide was heated to 140° for
24 hours under argon in 7.5 ml of ethylene glycol/water 2:1 in
25 the presence of 0.50 g (8.9 mmol) of potassium hydroxide. The mixture was left to cool and was poured into 75 ml of ice-water. After the addition of 25 ml of saturated sodium chloride solution the mixture was extracted three times with diethyl ether, the combined extracts were washed once with saturated sodium
30 chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 20 ml of diethyl ether and added dropwise to a suspension of 406 mg (3.5 mmol) of fumaric acid in 80 ml of diethyl ether. The solvent was removed in a vacuum and the residue was recrystallized from
35 90 ml of ethanol/ethyl acetate 5:4. 556 mg (45%) of 2-(8-chloro-4,5-dihydro-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) with m.p. 179-180° were obtained as white crystals.

Example 64

- a) A solution of 23.9 g (0.145 mol) of 4-thiochromanone, 30 ml (0.35 mol) of 3-buten-2-ol and 240 mg of p-toluenesulphonic acid in 30 ml of 2,2-dimethoxypropane and 240 ml of anhydrous toluene was boiled under reflux for 20 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 5:1). 15.3 g (48%) of (RS)-2-(2-buten-1-yl)-4-thiochromanone were obtained as a yellow oil.
- b) An ozone stream (3 g ozone/hour) was conducted while stirring for 15 minutes through a solution, cooled to -70° , of 3 g (13.7 mmol) of (RS)-2-(2-buten-1-yl)-4-thiochromanone in 100 ml of anhydrous dichloromethane and 30 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 2 ml (20.5 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was subsequently evaporated in a vacuum, the residue was treated with 50 ml of dichloromethane and, after the addition of 5 ml of water and 5 ml of trifluoroacetic acid, stirred at room temperature for 1 hour. The mixture was subsequently poured into 50 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 50 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 80 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There were obtained 2.8 g (99%) of 2-(2-oxoethyl)-4-thiochromanone as a yellow oil which was used in the next reaction without further recrystallization.
- c) A solution of 2 g (9.7 mmol) of 2-(2-oxoethyl)-4-thiochromanone and 120 mg of p-toluenesulphonic acid in 100 ml of anhydrous toluene was heated on a water separator. A solution of 2.9 g (38.6 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution

over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 20 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). There were obtained 1.8 g (76%) of (RS)-1-(1,4-dihydro-[1]benzothiopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol as a pale brown solid which was used in the next reaction without further recrystallization.

d) 1.15 ml (14.7 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 1.8 g (7.3 mmol) of (RS)-1-(1,4-dihydro-[1]benzothiopyrano[4,3-b]pyrrol-1-yl)-propan-2-ol and 4.1 ml (29.3 mmol) of triethylamine in 50 ml of anhydrous dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 180 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 70 ml of diethyl ether. The combined organic phases were washed with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 50 ml of anhydrous dimethylformamide, treated with 0.96 g (14.7 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 17 hours. After cooling the solution was poured into 100 ml of water and extracted twice with 120 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.17 g (59%) of (RS)-1-(2-azido-propyl)-1,4-dihydro-[1]benzothiopyrano[4,3-b]pyrrole were obtained as a light yellow oil.

e) 1.17 g (4.3 mmol) of (RS)-1-(2-azido-propyl)-1,4-dihydro-[1]benzothiopyrano[4,3-b]pyrrole dissolved in 30 ml of anhydrous tetrahydrofuran were added dropwise while stirring to a sus-

pension of 247 mg (6.49 mmol) of lithium aluminium hydride in 30 ml of anhydrous tetrahydrofuran. The mixture was subsequently boiled under reflux for 2 hours. Hydrolysis was effected with 20% aqueous tetrahydrofuran. The liquid phase was separated and the residue was boiled with 50 ml of 20% aqueous tetrahydrofuran for a further 15 minutes. The combined solutions were treated with 100 ml of diethyl ether, the organic phase was separated and the aqueous phase was extracted twice with 50 ml of diethyl ether each time. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. There were obtained 970 mg (92%) of a colourless oil which was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 461 mg (3.97 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 3 hours and the light yellow crystals were subsequently filtered off. 1.2 g (77%) of (RS)-1-(1,4-dihydro-[1]benzothiopyrano[4,3-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 201° were obtained.

Example 65

a) A solution of 29.5 g (0.22 mol) of 1-indanone, 73.5 ml (0.65 mol) 3-buten-2-ol, 77.0 ml (0.63 mol) of 2,2-dimethoxypropane and 400 mg of p-toluenesulphonic acid in 400 ml of toluene was boiled under reflux for 24 hours. After cooling the solution was washed with 100 ml of saturated sodium hydrogen carbonate solution. The aqueous washing was extracted with 150 ml of ethyl acetate and the organic phases were combined, dried with magnesium sulphate and evaporated in a vacuum. Purification on silica gel (hexane/diethyl ether 7:1) yielded 19.8 g (48%) of (RS)-2-(2-buten-1-yl)-1-indanone as a pale yellow oil.

b) Ozone (3 g ozone/hour) was conducted while stirring for 120 minutes through a solution, cooled to -70°, of 19.8 g (0.11 mol) of (RS)-2-(2-buten-1-yl)-1-indanone in 700 ml of anhydrous dichloromethane and 200 ml of anhydrous methanol.

Subsequently, the solution was flushed with oxygen and then 11.0 ml (0.15 mol) of dimethyl sulphide were added to the cold solution. The solution came to room temperature overnight and was evaporated in a vacuum. The residue was purified on silica gel (ethyl acetate). 10.1 g (43%) of (RS)-2-(2,2-dimethoxy-ethyl)-1-indanone were obtained as a yellow oil.

c) A solution of 1.7 g (7.7 mmol) of (RS)-2-(2,2-dimethoxy-ethyl)-1-indanone, 25 g (0.25 mol) of N-acetylenehydrazine and 30 ml of trifluoroacetic acid in 500 ml of ethanol was boiled under reflux for 96 hours. After cooling and adding 21.5 g of sodium hydroxide in 100 ml of water the mixture was evaporated to about 100 ml. The mixture was treated with 200 ml of ethyl acetate and washed in succession with 100 ml of saturated sodium chloride solution, 1N hydrochloric acid (4 x 100 ml), 2N sodium hydroxide solution (4 x 100 ml) and 100 ml of water. The aqueous washings were extracted with 100 ml of ethyl acetate and the organic phases were combined, dried with magnesium sulphate and evaporated in a vacuum. The residue was purified on basic aluminium oxide (III, dichloromethane) and then on silica gel (ethyl acetate). 0.4 g (22%) of N-[2-(1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethyl]-acetamide was obtained as a colourless solid.

d) 385 mg (1.6 mmol) of N-[2-(1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethyl]-acetamide were heated to 140° for 22 hours under argon in 6 ml of ethylene glycol/water 2:1 in the presence of 540 mg (9.6 mmol) of potassium hydroxide. The mixture was left to cool and was treated with 20 ml of semi-saturated sodium chloride solution. The mixture was extracted three times with diethyl ether and the combined extracts were dried over sodium sulphate, filtered and evaporated. The brown oil was dissolved in 5 ml of methanol and treated with 185 mg (1.59 mmol) of fumaric acid, whereby pale brown crystals separated. These were dissolved in 50 ml of warm methanol. After cooling to room temperature the product was crystallized by the slow addition of 50 ml of diethyl ether. The product obtained was heated in 15 ml of tert.-butyl methyl ether for 1

hour, filtered off under suction and dried in a vacuum. 220 mg (53%) of 2-(1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-ethylamine fumarate with m.p. 201-202° were obtained.

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Example 66

a) A solution of 29.6 g (0.20 mol) of benzosuberone and 60.9 ml (0.80 mol) of N,N-dimethylhydrazine in 150 ml of anhydrous ethanol was boiled under reflux for 3 days. Ethanol and excess N,N-dimethylhydrazine were removed in a vacuum and the residue was taken up in dichloromethane and dried with magnesium sulphate. Distillation over a 10 cm Vigreux column yielded 32.9 g (83%) of benzosuberone N',N'-dimethylhydrazone as a yellow oil. B.p.: 78-81°C/0.2 mbar.

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b) A solution of 33.6 g (0.17 mol) of benzosuberone N',N'-dimethylhydrazone and 29.9 ml (0.20 mol) of N,N,N',N'-tetramethylethylenediamine in 400 ml of absolute tetrahydrofuran was cooled to -70° under argon and 106 ml of a 1.6 M solution of n-butyllithium in hexane was added dropwise within 15 minutes. The mixture was then stirred at -70° for 30 minutes, left to warm to -30° and treated dropwise at this temperature with 23.4 ml (0.20 mol) of bromoacetaldehyde dimethyl acetal. After stirring at -30° for 1.5 hours the mixture was left to warm to room temperature overnight and the solution was treated with 500 ml of water. The mixture was extracted with ethyl acetate (1 x 500, 2 x 100 ml) and the organic phases were combined, dried with magnesium sulphate and evaporated in a vacuum. After column chromatography on silica gel (hexane/ethyl acetate 10:1-3:1) 37.7 g (78%) of (RS)-2-(2,2-dimethoxyethyl)-benzosuberone N',N'-dimethylhydrazone were obtained as an orange-yellow oil.

c) A suspension of 37.7 g (0.13 mol) of (RS)-2-(2,2-dimethoxyethyl)-benzosuberone N',N'-dimethylhydrazone, 30.2 g (0.37 mol) of sodium acetate and 78.8 g (0.37 mol) of sodium periodate in 2000 ml of tetrahydrofuran was treated with 300 ml of acetic acid and stirred at 50° overnight. The mixture was cooled, poured into 300 ml of water and extracted with

dichloromethane (1 x 3000, 2 x 1000 ml). The organic phases were combined, dried with magnesium sulphate and concentrated in a vacuum. Column chromatography on silica gel (hexane/ethyl acetate 2:1) yielded 8.2 g (25%) of (RS)-2-(2,2-dimethoxyethyl)-benzosuberone as a red oil in addition to 9.7 g (26%) of starting material.

d) 8.2 g of (RS)-2-(2,2-dimethoxyethyl)-benzosuberone were chromatographed over a column of oxalic acid solution adsorbed on silica gel (180 g of silica gel/20 ml of 10% oxalic acid solution). 6.2 g (90%) of (RS)-2-(2-oxoethyl)-benzosuberone were obtained as a red oil.

e) A solution of 6.2 g (30 mmol) of (RS)-2-(2-oxoethyl)-benzosuberone and 3.3 g (32 mmol) of N-acetylenediamine in 50 ml of anhydrous dichloromethane was treated with 50 g of molecular sieve 4Å and boiled under reflux overnight. After cooling the mixture was filtered over Celite, evaporated in a vacuum and the residue was recrystallized from hexane/ethyl acetate 2:1. 4.0 g (50%) of N-[2-(1,4,5,6-tetrahydro-benzo[6,7]cyclohepta[1,2-b]pyrrol-1-yl)-ethyl]-acetamide were obtained as a colourless solid.

f) 1.80 g (6.7 mmol) of N-[2-(1,4,5,6-tetrahydro-benzo[6,7]cyclohepta[1,2-b]pyrrol-1-yl)-ethyl]-acetamide were heated to 140° for 24 hours under argon in 18 ml of ethylene glycol/water 2:1 in the presence of 1.0 g (17.8 mmol) of potassium hydroxide. The reaction mixture was left to cool and was poured into 140 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether and the combined extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The thus-obtained oil was chromatographed on 60 g of silica gel with methylene chloride/methanol 19:1. The crude product was dissolved in 5 ml of diethyl ether and treated with 505 mg (4.35 mmol) of fumaric acid in 10 ml of diethyl ether. The crystals were filtered off and recrystallized from 50 ml of ethyl acetate/ethanol 2:1. 1.65 g (72%) of 2-(1,4,5,6-tetra-

hydro-benzo[6,7]cyclohepta[1,2-b]pyrrol-1-yl)-ethylamine fumarate (1:1) were obtained as white crystals with m.p. 175-176°.

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Example 67

10 a) A solution of 26.4 g (0.16 mol) of 7-methoxy-1-indanone, 33.6 ml (0.39 mol) of 3-buten-2-ol and 265 mg of p-toluene-sulphonic acid in 33.6 ml of 2,2-dimethoxypropane and 265 ml of anhydrous toluene was boiled under reflux for 17 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether, 5:1). 9.9 g (28%) of (RS)-2-(2-buten-1-yl)-7-methoxy-1-indanone were obtained as a yellow oil.

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15 b) An ozone stream (3 g ozone/hour) was conducted while stirring for 45 minutes through a solution, cooled to -70°, of 9.9 g (45.8 mmol) of (RS)-2-(2-buten-1-yl)-7-methoxy-1-indanone in 200 ml of anhydrous dichloromethane and 100 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 5 ml (67.7 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated 25 with 200 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 3 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further 100 ml of 30 water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was crystallized from ethyl acetate/hexane. 6.6 g (71%) of (RS)- 35 2-(2-oxoethyl)-7-methoxy-1-indanone were obtained as a white solid with m.p. 102°.

- c) A solution of 2.04 g (10 mmol) of (RS)-2-(2-oxoethyl)-7-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.0 g (40 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 2:3). There was obtained 1.1 g (45%) of (RS)-1-(8-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol as a brown oil which was used directly in the next reaction.
- d) 0.7 ml (9.0 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.1 g (4.5 mmol) of (RS)-1-(8-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.5 ml (18.0 mmol) of triethylamine in 25 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 140 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 526 mg (8.1 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 29 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 140 ml of water and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.68 g (56%) of (RS)-1-(2-azido-propyl)-8-methoxy-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

- e) 0.67 g (2.5 mmol) of (RS)-1-(2-azido-propyl)-8-methoxy-1,4-dihydro-indeno[1,2-b]-pyrrole dissolved in 25 ml of anhydrous ethanol was hydrogenated on 67 mg of platinum oxide for 5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 273 mg (2.35 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 22 hours and the white crystals were subsequently filtered off. 559 mg (74%) of (RS)-2-(8-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 193° were obtained.

Example 68

- 15 a) A solution of 23.3 g (0.105 mol) of (RS)-3-phenyl-1-tetralone, 21.6 ml (0.25 mol) of 3-buten-2-ol and 230 mg of p-toluenesulphonic acid in 21.6 ml of 2,2-dimethoxypropane and 230 ml of anhydrous toluene was boiled under reflux for 30 hours. The reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/diethyl ether 4:1). 11.8 g (41%) of (2RS/3RS)-2-(2-buten-1-yl)-3-phenyl-1-tetralone were obtained as a red oil.
- 25 b) An ozone stream (3 g ozone/hour) was conducted while stirring for 40 minutes through a solution, cooled to -70°, of 11.8 g (42.7 mmol) of (2RS/3RS)-2-(2-buten-1-yl)-3-phenyl-1-tetralone in 300 ml of anhydrous dichloromethane and 100 ml of anhydrous methanol. Subsequently, the solution was flushed with oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.45 ml (60.8 mmol) of dimethyl sulphide the mixture was stirred for 17 hours at room temperature. The reaction mixture was evaporated in a vacuum and the residue was treated with 300 ml of dichloromethane and, after the addition of 30 ml of water and 30 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further

100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude product obtained was purified by column chromatography on silica gel (toluene/ethyl acetate 9:1). 9.7 g (86%) of (2RS/3RS)-2-(2-oxoethyl)-3-phenyl-1-tetralone were obtained as a yellow oil.

c) A solution of 2 g (7.6 mmol) of (2RS/3RS)-2-(2-oxoethyl)-3-phenyl-1-tetralone and 80 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.18 g (29.0 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 30 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:9). There were obtained 1.04 g (45%) of (2RS/4RS)-1-(4,5-dihydro-4-phenyl-1-H-benz[g]indol-1-yl)-propan-2-ol as a brown oil which was used directly in the next reaction.

d) 0.53 ml (6.8 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.04 g (3.4 mmol) of (2RS/4RS)-1-(4,5-dihydro-4-phenyl-1-H-benz[g]indol-1-yl)-propan-2-ol and 1.9 ml (13.6 mmol) of triethylamine in 30 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 130 ml of diethyl ether. The combined organic phases were washed with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 25 ml of anhydrous dimethylformamide, treated with 0.45 g (6.8 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 6 hours. After cooling the solution was poured into

140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 100 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution
5 was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 473 mg (42%) of (2RS/4RS)-1-(2-azido-propyl)-4,5-dihydro-4-phenyl-1H-benz[g]indole were obtained as a colourless oil.

10 e) 473 mg (1.44 mmol) of (2RS/4RS)-1-(2-azido-propyl)-4,5-dihydro-4-phenyl-1H-benz[g]indole dissolved in 20 ml of anhydrous ethanol were hydrogenated on 50 mg of platinum oxide for 5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The
15 colourless oil obtained was dissolved in 40 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 148 mg (1.28 mmol) of fumaric acid in 5 ml of methanol. - The mixture was stirred at room temperature for 7 hours and the white crystals were subsequently filtered off. 446 mg (74%) of
20 (2RS/4RS)-2-(4,5-dihydro-4-phenyl-1H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:1) with m.p. 187° were obtained.

Example 69

25 a) A solution of 20 g (96 mmol) of (RS)-3-phenyl-1-indanone, 20 ml (0.23 mol) of 3-buten-2-ol and 200 mg of p-toluene-sulphonic acid in 20 ml of 2,2-dimethoxypropane and 200 ml of anhydrous toluene was boiled under reflux for 22 hours. The reaction mixture was subsequently concentrated in a vacuum and
30 purified by column chromatography on silica gel (hexane/ethyl acetate 5:1). 10 g (40%) of (2RS/3RS)-2-(2-buten-1-yl)-3-phenyl-1-indanone were obtained as a yellow oil.

b) An ozone stream (3 g ozone/hour) was conducted while
35 stirring for 40 minutes through a solution, cooled to -70°, of 10 g (38.1 mmol) of (2RS/3RS)-2-(2-buten-1-yl)-3-phenyl-1-indanone in 200 ml of anhydrous dichloromethane and 70 ml of anhydrous methanol. Subsequently, the solution was flushed was

oxygen for 5 minutes and with argon for 10 minutes. After the addition of 4.3 ml (58.2 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated
5 with 150 ml of dichloromethane and, after the addition of 20 ml of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 1 hour. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further
10 100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate and concentrated in a vacuum. There were obtained 9.5 g (99%) of (2RS/3RS)-2-(2-oxoethyl)-3-phenyl-1-
15 indanone as an oil which was used in the next reaction without further purification.

c) A solution of 3.0 g (12 mmol) of (2RS/3RS)-2-(2-oxoethyl)-3-phenyl-1-indanone and 100 mg of p-toluenesulphonic
20 acid in 100 ml of anhydrous toluene was heated on a water separator. A solution of 3.6 g (48 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 35 minutes, during which the
25 solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:1). There were obtained 2.4 g (69%) of (2RS/4RS)-1-(4-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol as an oil which was used directly in the next
30 reaction.

d) 1.24 ml (15.9 mmol) of methanesulphonyl chloride were added dropwise while stirring to a solution, cooled to 0°, of 2.3 g (7.9 mmol) of (2RS/4RS)-1-(4-phenyl-1,4-dihydro-indeno[1,2-
35 b]pyrrol-1-yl)-propan-2-ol and 4.46 ml (31.8 mmol) of triethylamine in 60 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed

twice with 70 ml of saturated sodium hydrogen carbonate solution each time and the combined aqueous phases were extracted once with 140 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 60 ml of anhydrous dimethylformamide, treated with 884 mg (13.6 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 16 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each time. The combined organic phases were washed once with 140 ml of water and with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 1.22 g (49%) of (2RS/4RS)-1-(2-azido-propyl)-4-phenyl-1,4-dihydro-indeno[1,2-b]-pyrrole were obtained as a light brown oil.

e) 1.2 g (3.8 mmol) of (2RS/4RS)-1-(2-azido-propyl)-4-phenyl-1,4-dihydro-indeno[1,2-b]-pyrrole dissolved in 50 ml of anhydrous ethanol were hydrogenated on 120 mg of platinum oxide for 5 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 100 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 480 mg (4.13 mmol) of fumaric acid in 20 ml of methanol. The mixture was stirred at room temperature for 16 hours and the crystals were subsequently filtered off. 1.04 g (65%) of (2RS/4RS)-2-(4-phenyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.86) with m.p. 191° were obtained.

Example 70

a) 13.7 g (77.0 mmol) of 8-methoxy-1-tetralone were dissolved in 140 ml of toluene under argon and added to 13.3 ml (155 mmol) of 3-buten-2-ol, 14.2 ml (116 mmol) of 2,2-dimethoxypropane and 300 mg of p-toluenesulphonic acid. The

reaction solution was heated to reflux for 90 hrs. The solvent was removed in a vacuum and the residue was chromatographed on 500 g of silica gel firstly with hexane/ethyl acetate 9:1, then with hexane/ethyl acetate 4:1 and finally with hexane/ethyl acetate 1:1. In addition to large amounts of unreacted educt (8.3 g) there were obtained 3.95 g (22%) of 2-(2-buten-1-yl)-8-methoxy-1-tetralone as a yellow oil.

b) 11.4 g (49.5 mmol) of 2-(2-buten-1-yl)-8-methoxy-1-tetralone were dissolved in a mixture of 340 ml of dichloromethane and 100 ml of methanol, cooled to -75° and the double bond was ozonized in the usual manner. After flushing the reaction mixture with oxygen and argon 7.2 ml (99.0 mmol) of dimethyl sulphide were added dropwise. The mixture was left to warm slowly to room temperature and was stirred for a further 17 hrs. The solvent was removed in a vacuum and the residue was taken up in 200 ml of diethyl ether and washed with water. Drying with sodium sulphate, filtration and evaporation gave 10.6 g of a mixture of dimethyl acetal and aldehyde. 7.0 g of this mixture were dissolved in 70 ml of methylene chloride and added to a mixture of 8.4 ml of 10% aqueous oxalic acid, 80 g of silica gel and 210 ml of dichloromethane. The mixture was stirred at room temperature for 2 hours. 5.6 g of 8-methoxy-2-(2-oxoethyl)-1-tetralone were obtained as a pale brown oil by extraction with dichloromethane/diethyl ether 9:1.

c) 400 mg (1.8 mmol) of 8-methoxy-2-(2-oxoethyl)-1-tetralone were heated to reflux for 15 minutes under argon with 205 mg (2.0 mmol) of N-acetylenediamine in 8 ml of toluene. The solvent was removed in a vacuum and the residue was chromatographed on 40 g of silica gel with hexane/ethyl acetate 1:1 and then with ethyl acetate. 280 mg (54%) of N-[2-(4,5-dihydro-9-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were obtained as yellowish crystals with m.p. $132-133^{\circ}$.

d) 2.3 g (8.0 mmol) of N-[2-(4,5-dihydro-9-methoxy-1H-benz[g]indol-1-yl)ethyl]-acetamide were heated to 140° for 16 hours under argon in 23 ml of ethylene glycol/water 2:1 in the

presence of 2.70 g (48.2 mmol) of potassium hydroxide. The reaction mixture was left to cool and was poured into 200 ml of semi-concentrated sodium chloride solution. The mixture was extracted three times with diethyl ether and the combined
5 extracts were washed once with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The crude product was dissolved in 20 ml of methanol and treated with 0.93 g (8.0 mmol) of fumaric acid. The separated crystals were recrystallized from a total of 70 ml of methanol. 1.76 g
10 (61%) of 2-(4,5-dihydro-9-methoxy-1H-benz[g]indol-1-yl)-ethylamine fumarate (1:1) were obtained as yellowish crystals with m.p. 184-185°.

Example 71

15

a) A solution of 21.5 g (0.13 mol) of 4-methoxy-1-indanone, 27.4 ml (0.32 mol) of 3-buten-2-ol and 210 mg of p-toluene-sulphonic acid in 27.4 ml of 2,2-dimethoxypropane and 210 ml of anhydrous toluene was boiled under reflux for 16 hours. The
20 reaction mixture was subsequently concentrated in a vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate 9:1). 6.42 g (23%) of (RS)-2-(2-buten-1-yl)-4-methoxy-1-indanone were obtained as a yellow oil.

25

b) An ozone stream (3 g ozone/hour) was conducted while stirring for 35 minutes through a solution, cooled to -70°, of 6.42 g (29.7 mmol) of (RS)-2-(2-buten-1-yl)-4-methoxy-1-indanone in 180 ml of anhydrous dichloromethane and 60 ml of anhydrous methanol. Subsequently, the solution was flushed with
30 oxygen for 5 minutes and with argon for 10 minutes. After the addition of 3.3 ml (44.7 mmol) of dimethyl sulphide the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated in a vacuum, the residue was treated with 200 ml of dichloromethane and, after the addition of 20 ml
35 of water and 20 ml of trifluoroacetic acid, stirred at room temperature for 2 hours. The mixture was subsequently poured into 100 ml of water and neutralized by the spatula-wise addition of sodium hydrogen carbonate while stirring. A further

100 ml of water were added, the phases were separated and the aqueous phase was extracted twice with 150 ml of dichloromethane each time. The combined organic phases were dried over magnesium sulphate, concentrated in a vacuum and the crude
5 product obtained was crystallized from ethyl acetate/hexane. 5.1 g (84%) of (RS)-2-(2-oxoethyl)-4-methoxy-1-indanone were obtained as a white solid with m.p. 71°.

c) A solution of 2.04 g (10 mmol) of (RS)-2-(2-oxoethyl)-4-methoxy-1-indanone and 80 mg of p-toluenesulphonic acid in
10 90 ml of anhydrous toluene was heated on a water separator. A solution of 3.13 g (41.7 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture
15 was boiled for a further 35 minutes, during which the solvent was reduced to a volume of 25 ml. The cooled reaction mixture was purified by column chromatography on silica gel (ethyl acetate/toluene 1:4). There was obtained 0.7 g (29%) of (RS)-1-(5-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol
20 as a brown oil which was used directly in the next reaction.

d) 0.45 ml (5.77 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 0.7 g (2.9 mmol) of (RS)-1-(5-methoxy-1,4-dihydro-indeno[1,2-
25 b]pyrrol-1-yl)-propan-2-ol and 1.6 ml (11.5 mmol) of triethylamine in 20 ml of dichloromethane and the mixture was stirred at this temperature for a further 1.5 hours. The reaction mixture was subsequently diluted with 200 ml of diethyl ether, washed twice with 70 ml of saturated sodium hydrogen carbonate solu-
30 tion each time and the combined aqueous phases were extracted once with 140 ml of diethyl ether. The combined organic phases were washed with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 20 ml of anhydrous di-
35 methylformamide, treated with 366 mg (5.6 mmol) of sodium azide and the reaction mixture was heated to 60° while stirring for 18 hours. After cooling the solution was poured into 140 ml of water and extracted twice with 140 ml of diethyl ether each

time. The combined organic phases were washed once with 140 ml of water and once with 140 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was
5 purified by column chromatography on silica gel (toluene). 0.55 g (73%) of (RS)-1-(2-azido-propyl)-5-methoxy-1,4-dihydro-indeno[1,2-b]-pyrrole was obtained as a colourless oil.

e) 0.54 g (2.0 mmol) of (RS)-1-(2-azido-propyl)-5-methoxy-
10 1,4-dihydro-indeno[1,2-b]-pyrrole dissolved in 20 ml of anhydrous ethanol was hydrogenated on 54 mg of platinum oxide for 17 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 50 ml of anhydrous diethyl
15 ether, filtered and treated while stirring with a solution of 110 mg (0.95 mmol) of fumaric acid in 10 ml of methanol. The mixture was stirred at room temperature for 22 hours and the white crystals were subsequently filtered off. 500 mg (83%) of (RS)-2-(5-methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-
20 methyl-ethylamine fumarate (1:0.5) with m.p. 194° were obtained.

Example 72

a) A solution of 0.95 g (3.1 mmol) of (2RS/4RS)-2-(4,5-
25 dihydro-4-phenyl-1-H-benz[g]indol-1-yl)-1-methyl-ethylamine in 15 ml of anhydrous pyridine was treated with 15 ml of acetic anhydride and heated to 50° for 30 minutes while stirring. The reaction mixture was subsequently poured on to ice and treated with 70 ml of saturated sodium hydrogen carbonate solution. The
30 mixture was extracted twice with 100 ml of dichloromethane each time and the combined organic phases were washed once with cold 3N sulphuric acid and once with cold saturated sodium hydrogen carbonate solution. After drying the solution over magnesium sulphate the solvent was drawn off in a vacuum and the
35 residue was taken up with 40 ml of anhydrous dioxan. 729 mg (3.21 mmol) of DDQ were added and the mixture was boiled under reflux for 1 hour. Subsequently, the reaction mixture was concentrated in a vacuum and the residue was purified by column

chromatography on silica gel (dichloromethane/methanol 20:1). There was obtained 0.69 g (64%) of (RS)-N-[2-(4-phenyl-1-H-benz[g]indol-1-yl)-1-methyl-ethyl]-acetamide as a pale brown solid which was used in the next reaction without further
5 recrystallization.

b) A mixture of 670 mg (1.96 mmol) of (RS)-N-[2-(4-phenyl-1-H-benz[g]indol-1-yl)-1-methyl-ethyl]-acetamide, 1.32 g (23.4 mmol) of potassium hydroxide in 15 ml of water and
10 30 ml of ethylene glycol was boiled under reflux for 46 hours. The reaction mixture was subsequently poured into 80 ml of saturated sodium chloride solution and extracted twice with 80 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of saturated sodium chloride
15 solution and dried over magnesium sulphate. After concentration in a vacuum the residue was purified by column chromatography on silica gel (dichloromethane/methanol 9:1) and the resulting oil [308 mg (1.03 mmol)] was dissolved in 30 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution
20 of 119 mg (1.03 mmol) of fumaric acid in 6 ml of methanol. The mixture was stirred at room temperature for 20 hours and the white crystals were subsequently filtered off. 308 mg (41%) of (RS)-2-(4-phenyl-1-H-benz[g]indol-1-yl)-1-methyl-ethylamine fumarate (1:0.7) with m.p. > 230° were obtained.
25

Example 73

a) A solution of LDA, prepared at 0° from 3.12 ml (22 mmol) of diisopropylamine and 13.8 ml (22 mmol) of n-butyllithium
30 (1.6N in hexane), in 40 ml of anhydrous tetrahydrofuran was added dropwise while stirring during 10 minutes to a solution, cooled to -70°, of 2.96 g (18.3 mmol) of 6-methoxy-1-indanone in 300 ml of anhydrous tetrahydrofuran. After 15 minutes a solution of 1.62 ml (20.2 mmol) of chloroacetone in 40 ml of
35 anhydrous tetrahydrofuran was added dropwise to the solution during 5 minutes and the mixture was subsequently stirred at room temperature for 2 hours. The reaction mixture was poured on to 150 ml of ice, 150 ml of saturated sodium chloride

solution were added and the mixture was extracted twice with 300 ml of diethyl ether each time. The combined organic phases were washed once with 200 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane/diethyl ether 3:2, then 2:3). 1.8 g (45%) of (RS)-6-methoxy-2-(2-oxopropyl)-1-indanone were obtained as a red oil.

10 b) A solution of 1.8 g (8.3 mmol) of (RS)-6-methoxy-2-(2-oxopropyl)-1-indanone and 70 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A solution of 2.48 g (33 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene were added dropwise to the boiling
15 solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 3 hours, during which the solvent was reduced to a volume of 30 ml. The cooled reaction mixture was purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.37 g (65%) of (RS)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as
20 a solid with m.p. 110°.

c) 0.81 ml (10.5 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of
25 1.35 g (5.3 mmol) of (RS)-1-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.9 ml (20.9 mmol) of triethylamine in 40 ml of dichloromethane. The reaction mixture was subsequently added to 70 ml of water, extracted twice with 100 ml of dichloromethane each time and the combined organic
30 phases were washed once with 70 ml of saturated sodium hydrogen carbonate solution and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.68 g (10.5 mmol)
35 of sodium azide and the reaction mixture was heated to 80° while stirring for 23 hours. After cooling the solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed

once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnesium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene).

- 5 0.93 g (62%) of (RS)-1-(2-azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

- d) 0.92 g (3.3 mmol) of (RS)-1-(2-azido-propyl)-7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 70 ml of anhydrous ethanol was hydrogenated on 90 mg of platinum oxide for 16 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 160 mg (1.4 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 17 hours and the white crystals were subsequently filtered off. 800 mg (78%) of (RS)-2-(7-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 187-188° were obtained.

Example 74

- 25 a) A solution of LDA, prepared at 0° from 4.25 ml (30 mmol) of diisopropylamine and 18.8 ml (30 mmol) of N-butyllithium (1.6N in hexane), in 60 ml of anhydrous tetrahydrofuran was added dropwise while stirring during 15 minutes to a solution, cooled to -70°, of 3.24 g (20 mmol) of 5-methoxy-1-indanone in 30 350 ml of anhydrous tetrahydrofuran. After 45 minutes a solution of 1.6 ml (20 mmol) of chloroacetone in 60 ml of anhydrous tetrahydrofuran was added dropwise to the solution during 15 minutes and the mixture was subsequently stirred at room temperature for 2 hours. The reaction mixture was poured on to 150 ml of ice, 150 ml of saturated sodium chloride solution were added and the mixture was extracted twice with 300 ml of diethyl ether each time. The combined organic phases were washed once with 200 ml of saturated sodium chloride

solution, dried over magnesium sulphate and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane/diethyl ether 3:7). 1.4 g (32%) of (RS)-5-methoxy-2-(2-oxopropyl)-1-indanone were
5 obtained as a solid with m.p. 73°.

b) A solution of 1.2 g (5.5 mmol) of (RS)-5-methoxy-2-(2-oxopropyl)-1-indanone and 60 mg of p-toluenesulphonic acid in 70 ml of anhydrous toluene was heated on a water separator. A
10 solution of 1.65 g (22 mmol) of (RS)-1-amino-2-propanol in 20 ml of anhydrous toluene was added dropwise to the boiling solution over a period of 5 minutes. Subsequently, the mixture was boiled for a further 3 hours, during which the solvent was reduced to a volume of 30 ml. The cold reaction mixture was
15 purified by column chromatography on silica gel (diethyl ether/hexane 7:3). 1.17 g (82%) of (RS)-1-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol were obtained as an oil.

c) 0.7 ml (9.0 mmol) of methanesulphonyl chloride was added dropwise while stirring to a solution, cooled to 0°, of 1.16 g (4.5 mmol) of (RS)-1-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-propan-2-ol and 2.5 ml (18 mmol) of triethylamine in 50 ml of dichloromethane and the solution was stirred
25 at this temperature for a further 1.5 hours. The reaction mixture was subsequently added to 70 ml of water, extracted twice with 100 ml of dichloromethane each time and the combined organic phases were washed once with 70 ml of saturated sodium hydrogen carbonate solution and once with 70 ml of
30 saturated sodium chloride solution, dried over magnesium sulphate and evaporated in a vacuum. The brown oil obtained was dissolved in 40 ml of anhydrous dimethylformamide, treated with 0.58 g (9.0 mmol) of sodium azide and the reaction mixture was heated to 80° while stirring for 16 hours. After cooling the
35 solution was poured into 70 ml of water and extracted twice with 100 ml of ethyl acetate each time. The combined organic phases were washed once with 70 ml of water and once with 70 ml of saturated sodium chloride solution, dried over magnes-

ium sulphate and the solution was concentrated in a vacuum. The brown oil obtained was purified by column chromatography on silica gel (toluene). 0.86 g (55%) of (RS)-1-(2-azido-propyl)-6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole was obtained as a colourless oil.

d) 0.85 g (3.0 mmol) of (RS)-1-(2-azido-propyl)-6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrole dissolved in 50 ml of anhydrous ethanol was hydrogenated on 85 mg of platinum oxide for 17 hours. The catalyst was subsequently filtered off, rinsed with ethanol and the solvent was drawn off in a vacuum. The colourless oil obtained was dissolved in 70 ml of anhydrous diethyl ether, filtered and treated while stirring with a solution of 155 mg (1.3 mmol) of fumaric acid in 15 ml of methanol. The mixture was stirred at room temperature for 19 hours and the white crystals were subsequently filtered off. 780 mg (83%) of (RS)-2-(6-methoxy-2-methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine fumarate (1:0.5) with m.p. 215° were obtained.

Example A

Tablets of the following composition were manufactured in a conventional manner:

	<u>mg/tablet</u>
Active substance	100
Powd. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Table weight	250

Example B

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Tablets of the following composition are manufactured in the usual manner:

5		<u>mg/tablet</u>
	Active substance	200
	Powd. lactose	100
10	White corn starch	64
	Polyvinylpyrrolidone	12
	Na carboxymethylstarch	20
	Magnesium stearate	4
	Table weight	400

15

Example C

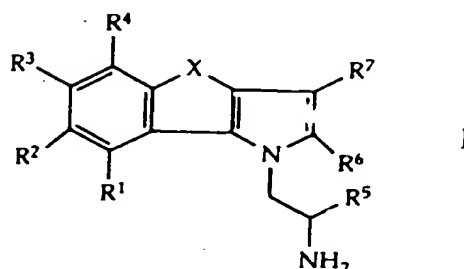
Capsules of the following composition are manufactured in the usual manner:

20		<u>mg/capsule</u>
	Active substance	50
	Cryst. lactose	60
25	Microcrystalline cellulose	34
	Talc	5
	Magnesium stearate	1
	Capsule fill weight	400

30 The active substance having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The finished mixture is filled into hard gelatine capsules of suitable size.

Claims

1. Compounds of the general formula



wherein

R¹ to R⁴ each signify hydrogen, halogen, lower alkyl, phenyl, cycloalkyl or lower alkoxy and R² additionally signifies lower alkoxycarbonyl, acyloxy or mesyloxy;

R⁵ to R⁷ each signify hydrogen or lower alkyl;

X signifies -CH₂CH(C₆H₅)-, -CH=C(C₆H₅)-, -YCH₂-, -CH=CH- or -(CR¹¹R¹²)_n;

R¹¹ and R¹² each signify hydrogen, phenyl, lower alkyl or halogen;

n signifies 1 to 3 and

Y signifies O or S,

as well as pharmaceutically usable salts of basic compounds of formula I with acids.

2. Compounds according to claim 1, wherein R⁵ signifies hydrogen or lower alkyl.

3. Compounds according to claim 2, wherein R⁵ signifies methyl.

4. Compounds according to claim 3, wherein R¹, R³ and R⁴ signify hydrogen and R² signifies halogen, lower alkyl or methoxy.

5. (S)-2-(4,4,7-Trimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

6. (S)-2-(7-Methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

7. (S)-2-(7-Ethyl-4,4-dimethyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

8. (S)-2-(7-Methyl-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

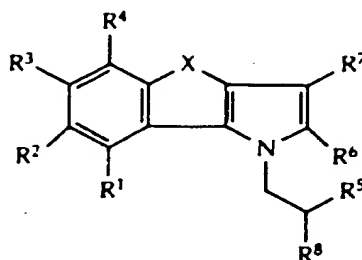
9. (S)-2-(7-Brom-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

10. (S)-2-(7-Methoxy-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

11. (S)-2-(7-Chloro-1,4-dihydro-indeno[1,2-b]pyrrol-1-yl)-1-methyl-ethylamine.

12. (S)-2-(8-Methoxy-1H-benz[g]indol-1-yl)-1-methyl-ethylamine.

13. Compounds of the general formula



II

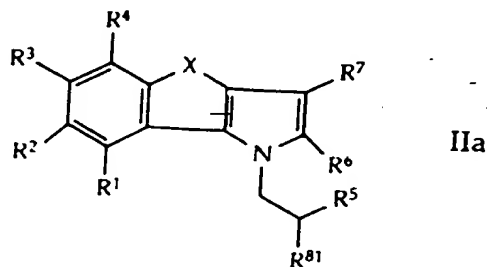
wherein R¹ to R⁷ and X have the significances given in claim 1 and R⁸ signifies a residue convertible into an amino group or a hydroxy group.

14. Compounds according to any one of claims 1 to 12 for use as therapeutically active substances.

15. Compounds according to any one of claims 1-12 for use as therapeutically active substances for the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility

16. A process for the manufacture of compounds according to any one of claims 1 to 12, which process comprises

a) converting a compound of the general formula



wherein R^1 to R^7 and X have the significances given in claim 1 and R^{81} signifies a residue convertible into an amino group,

into a corresponding amino compound and

b) if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

17. A medicament containing a compound according to any one of claims 1 to 12 and a therapeutically inert carrier material.

18. A medicament according to claim 17 for the treatment
5 or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive compulsive disorders, social phobias or
10 panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis,
15 stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

19. The use of compounds according to any one of claims 1 to 12 in the treatment or prevention of illnesses.

20

20. The use of compounds according to any one of claims 1 to 12 in the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other
25 conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia
30 etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

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21. The use of compounds according to any one of claims 1 to 12 for the manufacture of medicaments for the treatment or prevention of central nervous disorders such as depressions,

bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive compulsive disorders, social phobias or
5 panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis,
10 stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

22. Compounds in accordance with any one of claims 1-12, whenever prepared according to the process as claimed in claim 16 or by an obvious chemical equivalent thereof.

23. The invention as hereinbefore described.

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24. A method of treating or preventing of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; damages of the nervous system by trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility, which comprises administering to a patient requiring such treatment an effective amount of a compound in accordance with any one of claims 1-12.

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